

**PREVALENCE, RISK FACTORS
AND DETECTION OF LEFT
VENTRICULAR DYSFUNCTION IN
THE COMMUNITY**

Canberra Heart Study

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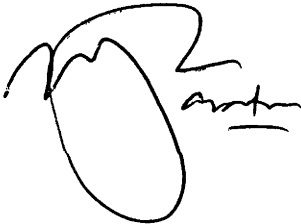
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DECLARATION

This work presented in the thesis describes the results of research carried out in the National Centre for Epidemiology and Population Health, Australian National University and the Department of Cardiology, Canberra Hospital, Australia, between February 2002 and July 2004.

The results presented in this thesis are my own work accomplished under the supervision of Professors Niels G. Becker, Wayne T. Smith and Anthony J. McMichael. This material has not been submitted either in whole or in part for a degree at this or any other university.

October 2009

A handwritten signature in black ink, appearing to read 'Walter P Abhayaratna', with a large, stylized initial 'W' and a smaller signature 'Abhayaratna' below it.

Walter P Abhayaratna

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If I have seen further....it is by standing on the shoulders of giants

Sir Isaac Newton

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PUBLICATIONS AND PRESENTATIONS RELATED TO THIS THESIS

Seven manuscripts from this research have been submitted and/or accepted for publication in international peer-reviewed journals. Five original scientific papers correspond directly to each of the study chapters in the thesis (chapters 4, 5, 6, 7 and 8). Information from two review articles has been included in chapters 1 and 2. Conference presentations relating to these manuscripts are also detailed.

Publications in peer-reviewed journals

1. Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM, McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. *Med J Aust* 2006;184:151-154
2. Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* 2006;92:1259-64
3. Abhayaratna WP, Sriksalanukul W, Budge MM. Aortic Stiffness for the Detection of Preclinical Left Ventricular Diastolic Dysfunction: Pulse Wave Velocity versus Pulse Pressure. *J Hypertension* 2008;26:758-64.
4. Abhayaratna WP, Marwick TH, Becker NG, Jeffery IM, McGill DA, Smith WT. Detection of left ventricular systolic and diastolic dysfunction in the community with aminoterminal pro-B-Type natriuretic peptide. *Am Heart J* 2006;152:941-8

5. Abhayaratna WP, Marwick TH, Becker NG. Asymptomatic left ventricular diastolic dysfunction and risk of death in the community. Under review at: *Eur Heart J*.
6. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TSM. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;47:1018-23
7. Sakuragi S, Abhayaratna WP. Arterial Stiffness: Methods of Measurement, Physiologic Determinants and Prediction of Cardiovascular Outcomes. *Int J Cardiol* 2009: *in press*

Abstract presentations at national / international conferences

1. Walter P Abhayaratna, Wayne T. Smith, Thomas H. Marwick, Ian M. Jeffery, Darryl A. McGill, Niels G. Becker. Is Left Atrial Volume a Marker of Diastolic Burden in the Community?
European Society of Cardiology, Vienna, Austria, September, 2003
Cardiac Society of Australia and New Zealand, Brisbane, August 2004
2. Walter P Abhayaratna, Wayne T. Smith, Thomas H. Marwick, Ian M. Jeffery, Darryl A. McGill, Niels G. Becker. Population-based screening of left ventricular diastolic dysfunction with N-terminal pro-BNP (NT-BNP).
European Society of Cardiology, Vienna, Austria, September, 2003
Cardiac Society of Australia and New Zealand, Brisbane, August 2004

3. Walter P Abhayaratna, Wayne T. Smith, Niels G. Becker, Thomas H. Marwick, Ian M. Jeffery, Darryl A. McGill. Quantifying the Burden of Heart Failure in the Community: a Role for the American College of Cardiology/ American Heart Association (ACC/AHA) Heart Failure Staging Classification.
American Heart Association, Dallas, Texas, November 2005
4. Walter P Abhayaratna, Thomas H. Marwick, Wayne T. Smith, Niels G. Becker. Characteristics of Left Ventricular Diastolic Dysfunction in the Community.
American Heart Association, Dallas, Texas, November 2005
5. Walter P Abhayaratna, Wayne T. Smith, Niels G. Becker, Thomas H. Marwick, Ian M. Jeffery, Darryl A. McGill. Screening for Left Ventricular Dysfunction in the Community.
American College of Cardiology, Atlanta, Georgia, November 2006
6. Walter P Abhayaratna, Wayne T. Smith, Niels G. Becker, Thomas H. Marwick, Ian M. Jeffery, Darryl A. McGill. Use of Aminoterminal Pro-B-type Natriuretic Peptide (N-BNP) Levels for the Detection of Left Ventricular Systolic and Diastolic Dysfunction in the Community.
American College of Cardiology, Atlanta, Georgia, November 2006
7. Walter P Abhayaratna, Wayne T. Smith, Niels G. Becker. Predictors of diastolic dysfunction in the community.
World Congress of Cardiology, Barcelona, Spain, August 2006

8. Walter P. Abhayaratna, Wichat Srikusalanukul, Marc M. Budge. Characterizing the relationship between aortic stiffness and diastolic function: a population-based study of older adults.

American Heart Association, Chicago, Illinois, November 2006

9. Walter P. Abhayaratna, Wichat Srikusalanukul, Marc M. Budge. Aortic Stiffness for the Detection of Preclinical Left Ventricular Diastolic Dysfunction: Pulse Wave Velocity versus Pulse Pressure.

American Heart Association, New Orleans, Louisiana, November 2007

10. Walter P Abhayaratna, Katrina Hayes, Christine O'Reilly, Niels G. Becker. Asymptomatic left ventricular diastolic dysfunction and risk of death in the community.

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ABSTRACT

Heart failure (HF) is a growing public health problem. In developed countries, the number of hospital admissions due to HF has increased. This trend has been attributed to the ageing of our population and an increased number of people at risk for HF as a result of more efficacious treatment for systemic hypertension and acute myocardial infarction. The syndrome of HF is associated with substantial mortality and morbidity rates, and consumes a significant proportion of the health care budget in most developed countries. In 1993-94, the health care costs attributed to HF in Australia were estimated to be over AUD\$400 million. A significant proportion of this cost was due to hospitalisations. HF, under the umbrella of “cardiovascular disease”, has been nominated as a National Health Priority Area. Despite this fact, there are no population-based data regarding the prevalence of HF in Australia. Such descriptive epidemiological data are important for guiding health policy and monitoring trends of the impact of disease over time. This latter function can be used to assess the impact of primary preventive and illness care interventions at the population level.

Initial HF treatment studies have focused on patients with impaired left ventricular (LV) systolic function, as documented by a reduced LV ejection fraction (EF). These studies have confirmed the efficacy of medical therapy for symptomatic HF with reduced EF (HF-rEF) that results in the improvement of patient symptoms, quality of life and survival. In the last decade, there has been an increasing awareness regarding HF associated with LV diastolic dysfunction (DD). This awareness has been generated by the observation that approximately half the patients presenting with HF

to hospitals have “normal” EF (HF-NEF). Doppler echocardiography has provided a non-invasive means of evaluating diastolic function. At the time this research was proposed, there was no information on the burden of DD in the community from population-based studies using comprehensive echo-Doppler methods.

Recent echocardiographic surveys have confirmed that approximately half of the cases in the community with reduced EF are asymptomatic of the disease. Randomised controlled trials have shown that medical treatment for individuals with reduced EF in the preclinical phase of disease is also beneficial. However, there is a lack of readily available, inexpensive methods for identifying cases of preclinical LV dysfunction in the community. Previous studies have suggested that circulating biomarkers may play an important role as a marker for LV dysfunction in high-risk patients, but evidence from the general community was limited.

The thesis reviews the epidemiology of HF in the community. The changing epidemiology of HF and LV dysfunction in the era of non-invasive cardiac imaging is also reviewed, with much of the evidence arising during the period of this thesis (Chapter 1). This is followed by a review of the current Doppler echocardiographic methods for the assessment of diastolic function in Chapter 2. Evidence to support the use of non-imaging methods for the detection of LV function (circulating biomarkers and measurement of arterial stiffness) is presented. The third chapter details study methodologies, including issues relating to recruitment of a population-based cohort of over 1300 randomly selected Canberra residents of age 60-86 years; echocardiographic evaluation of cardiac function; and the assessment of circulating biomarkers, specifically the aminoterminal component of pro-B-type natriuretic

peptide (NT-proBNP), a protein secreted principally by the cardiac ventricles in response to elevated cardiac pressures and wall tension; and measurement of wave reflection-dependent (pulse pressure) and independent [carotid-femoral pulse wave velocity (PWV)] indexes of aortic stiffness by applanation tonometry.

The first Australian data on the prevalence of HF and LV systolic dysfunction ($EF < 50\%$) in the community are presented in Chapter 4. Of the 1275 participants who completed all study measurements, 72 (5.6%) subjects had clinical HF that had been previously diagnosed and confirmed by our assessment. A further 0.6% had evidence of structural heart disease and symptoms/signs of cardiac insufficiency without a previous diagnosis of clinical HF (i.e. undiagnosed clinical HF). Thus, overall the prevalence of clinical HF in the sample was 6.3%. Clinical HF increased in prevalence with advancing age (4-fold increase in prevalence from 60-64 to 80-86 years). Of the 75 subjects with LV systolic dysfunction, 44 (59%) were in the preclinical stage of disease. Based on these data, it is likely that diagnosed HF cases represent the “tip of the iceberg” for the national burden of HF and LV systolic dysfunction. Clinically identifiable HF cases can remain undiagnosed, and the majority of subjects with LV systolic dysfunction are preclinical.

One of the first estimates of the burden of DD in the community is presented in Chapter 5. The prevalence of any DD in our population-based sample was 35.6% and moderate-severe DD was 7.5%. Of those with moderate-severe DD, 84.7% had an $EF \geq 50\%$ and 77.2% were preclinical. Predictors of DD included increasing age; reduced EF; obesity; history of hypertension, diabetes and myocardial infarction. Moderate-severe DD with normal EF, although predominantly preclinical, was

independently associated with increased LV mass, left atrial (LA) volume, circulating NT-proBNP levels, and decreased quality of life. Extrapolating this data, it is likely that DD is common in the community and frequently unaccompanied by overt HF. Despite the lack of symptoms, advanced DD with normal EF is associated with reduced quality of life and structural abnormalities that reflect increased cardiovascular risk.

In Chapter 6, the utility of NT-proBNP to detect systolic and diastolic LV dysfunction in older adults was determined. Predictors of NT-proBNP included age, female gender, body mass index, and cardiorenal parameters (DD severity; LV mass and volume; right ventricular overload; decreasing EF and creatinine clearance). The performance of NT-proBNP to detect any degree of LV dysfunction, including mild DD, was poor (AUC 0.56-0.66). In contrast, the performance of NT-proBNP for the detection of $EF \leq 40\%$ and moderate-severe DD was strong with $AUC > 0.90$ regardless of age and gender. The ability of NT-proBNP to detect $EF \leq 40\%$ and/or moderate-severe DD was optimised by using age/gender-specific limits (men 60-74, 20pmol/L; women 60-74, 30pmol/L; ≥ 75 years, 45pmol/L). Of “false positive” tests, 88% (126/143) were explained after considering cardiorenal determinants of NT-proBNP levels. Based on these results, we concluded that NT-proBNP represents a suboptimal marker of mild LV dysfunction, but performs strongly as a marker of $EF \leq 40\%$ and/or moderate-severe DD in the community.

In chapter 7, the performances of indexes of aortic stiffness to detect preclinical DD were evaluated in a nested case-control study, using a stratified subsample of 233 participants of the study population with $EF \geq 45\%$ and without overt HF. Brachial

pulse pressure, central pulse pressure, and PWV progressively increased according to the severity of DD, independent of age and sex. The overall performance of PWV was superior to brachial pulse pressure [area under receiver operating characteristic curve (AUC): 0.70 versus 0.59, respectively; $P = 0.005$] and central pulse pressure (AUC: 0.70 versus 0.56, respectively; $P = 0.001$) for the detection of any DD. PWV appeared to be superior to central and brachial pulse pressure for the detection of DD in older adults with “preserved” EF.

Finally, a brief outline of future directions for this cohort study is provided.

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ABBREVIATIONS

A = peak late diastolic transmitral velocity

Aa = late diastolic mitral annular velocity

ACE = angiotensin converting enzyme

AIx = augmentation index

A reversal = pulmonary vein atrial reversal velocity

BMI = body mass index

BNP = B-type natriuretic peptide

BP = blood pressure

CAD = coronary artery disease

CrCl = creatinine clearance

CV = cardiovascular

D = pulmonary vein diastolic velocity

DD = left ventricular diastolic dysfunction

E = peak early diastolic transmitral velocity

EF = left ventricular ejection fraction

DD-NEF = left ventricular diastolic dysfunction with normal ejection fraction

Ea = peak early diastolic mitral annular velocity

HF = heart failure

HF-NEF = heart failure with normal ejection fraction

HF-rEF = heart failure with reduced ejection fraction

HT = systemic hypertension

LA = left atrium/atrial

LAVI = indexed left atrial volume

LV = left ventricle/ventricular

MBP = mean blood pressure

NT-proBNP = aminoterminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

PP = pulse pressure

PWV = pulse wave velocity

S = pulmonary vein systolic velocity

Sa = peak systolic mitral annular velocity

TDI = tissue Doppler imaging

PREFACE - INTRODUCTION AND AIMS OF THIS THESIS

Heart failure (HF) is a growing public health problem. In developed countries, the number of hospital admissions due to HF has increased. This trend has been attributed to the ageing of our population and an increased number of people at risk for HF as a result of more efficacious treatment for systemic hypertension and acute myocardial infarction. The syndrome of HF is associated with substantial mortality and morbidity rates, and consumes a significant proportion of the health care budget in most developed countries. In 1993-94, the health care costs attributed to HF were estimated to be over AUD\$400 million. A significant proportion of this cost was due to hospitalisations. HF, under the umbrella of 'cardiovascular disease', has been nominated as a National Health Priority Area. Despite this fact, there are no population-based data regarding the prevalence of HF in Australia. Such data are important for guiding health policy and monitoring trends of the impact of disease over time. In particular, the latter function can be used to assess the impact of primary preventive and illness care interventions at the population level. Therefore, the initial set of aims related to the thesis was to determine:

- What is the prevalence of HF and left ventricular (LV) systolic dysfunction in Australia? (addressed in chapter 4)
- What are the clinical characteristics of subjects with HF and LV systolic dysfunction? (addressed in chapter 4)

Initial HF treatment studies have focused on patients with impaired LV systolic function. These studies have confirmed the efficacy of medical therapy for symptomatic LV dysfunction that results in the improvement of patient symptoms,

quality of life and survival. In the last decade, there has been an increasing awareness regarding HF associated with LV diastolic dysfunction (DD). This awareness has been generated by the observation that approximately half the patients presenting with HF to hospitals have preserved LV systolic function. Doppler echocardiography has provided a non-invasive means of evaluating diastolic function. At the time this research was proposed, there was no information on the burden of DD in the community from population-based studies using comprehensive echo-Doppler methods. Thus, the next set of aims related to this thesis addressed the following questions:

- What is the prevalence of DD in the community? (addressed in chapter 5)
- What are the clinical characteristics of subjects with DD? (addressed in chapter 5)

Recent echocardiographic surveys have confirmed that approximately half of the cases in the community with LV systolic dysfunction are asymptomatic of the disease. Randomised controlled trials have shown that medical treatment for individuals with LV systolic dysfunction in the preclinical phase of disease is also beneficial. However, there is a lack of readily available, inexpensive methods for identifying cases of preclinical LV dysfunction in the community. Previous studies have suggested that circulating biomarkers may play an important role as a marker for LV dysfunction in high-risk patients, but evidence from the general community was limited at the time that the Canberra Heart Study was being designed. The final set of aims relating to this thesis addressed the general question:

- What non-imaging diagnostic methods could be used to detect LV dysfunction?

We specifically assessed the performances of circulating levels of aminoterminal pro-B-type natriuretic peptide (NT-proBNP), a protein secreted principally by the cardiac ventricles in response to elevated cardiac filling pressures and wall tension (addressed in chapter 6); and measurement of indexes of aortic stiffness by applanation tonometry (addressed in chapter 7).

Chapter 1: EPIDEMIOLOGY OF CHRONIC HEART FAILURE AND LEFT VENTRICULAR DYSFUNCTION

1.1 ABSTRACT

Heart failure (HF) is a growing public health problem. The syndrome of HF is associated with substantial mortality and morbidity rates, and consumes a significant proportion of the health care budget in most developed countries. In this chapter, the burden of HF in the community is examined; the pathophysiology of hypertensive heart disease and diastolic dysfunction (DD) is outlined; and the changing epidemiology of HF and left ventricular (LV) dysfunction in the era of non-invasive cardiac imaging is reviewed.

1.2 INTRODUCTION

Heart failure (HF) is a serious medical condition, with a poor prognosis. The prevalence and incidence of HF in the community has risen to “epidemic” proportions, and evidence suggests that the public health burden of HF will continue to grow.¹ In this chapter, I will outline how our understanding of basic fundamental concepts relating to the definition and mechanisms of HF have been guided by findings from epidemiological studies and facilitated by evolving medical technologies, particularly with the development and availability of non-invasive cardiac imaging such as echocardiography. Specifically, I will examine the burden of HF in the community; outline the pathophysiology of hypertensive heart disease and diastolic dysfunction (DD); and review the changing epidemiology of HF and left ventricular (LV) dysfunction in the era of non-invasive cardiac imaging

1.3 DEFINITION OF HEART FAILURE

Attempts to define HF have resulted in controversy, due to the complexity of the syndrome. HF is not a disease but rather a constellation of symptoms and signs caused by a blend of structural and functional changes to the heart, with haemodynamic and neurohumoral responses associated with these changes. Despite many efforts, there is no single definition for HF that has received universal acceptance. Table 1-1 lists selected definitions that have been proposed over the last 75 years. The definition for HF has evolved in parallel with advances in the understanding of syndrome pathophysiology.

Table 1-1 Definitions of heart failure

Thomas Lewis	1933	A condition in which the heart fails to discharge its contents adequately ²
T. Harrison	1936	A syndrome characterised by dyspnoea, rales at the lung bases, venous distension, engorgement of the viscera, and accumulation of fluid in the subcutaneous tissue and body cavities ²
Paul Wood	1950	A state in which the heart fails to maintain an adequate circulation for the needs of the whole body despite a satisfactory filling pressure ²
Eugene Braunwald	1980	A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues ²
P Poole-Wilson	1985	A clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses ²
Milton Packer	1992	A complex clinical syndrome characterised by abnormalities of left ventricular function and neurohumoral regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity ²
ESC Task Force	1995	Symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure ³
ACC/AHA Task Force	2001	A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood ⁴

Several conceptual models have been developed to illustrate the mechanisms of HF and to rationalise the opportunities for intervention, including screening and

prevention of the syndrome. Prior to 1980, HF was defined within the framework of a haemodynamic model, in which impaired myocyte contractility was considered to be the basis of HF. In this model, a decrease in cardiac performance results in symptoms on exertion initially but as cardiac haemodynamics worsen, the symptoms may appear at rest. The model remains useful for patients with advanced, decompensated HF but has been largely abandoned in favour of the neurohormonal model, in which structural changes to the heart are associated with activation of the sympathoadrenal (SAS) and renin-angiotensin-aldosterone (RAAS) systems, resulting in progressive cardiac remodelling. In the neurohormonal model, impairment of cardiac performance is a secondary phenomenon. The advantages of this model are that it allows classification of the syndrome at earlier stages of the disease process and also identifies a wider scope for pharmacological intervention.

1.4 DIAGNOSIS OF HEART FAILURE

1.4.1 Clinical guidelines for the identification of heart failure cases

A number of clinical guidelines for the diagnosis and management of HF have been published.⁵⁻⁷ The high frequency of updates is testimony to the large volume of research directed to this important field of medicine. There is consensus that a clinical diagnosis of HF is based on a complete history and examination followed by diagnostic testing, initially using readily available radiology and biochemistry assessments and subsequently with cardiac imaging (most often echocardiography) (Figure 1-1).

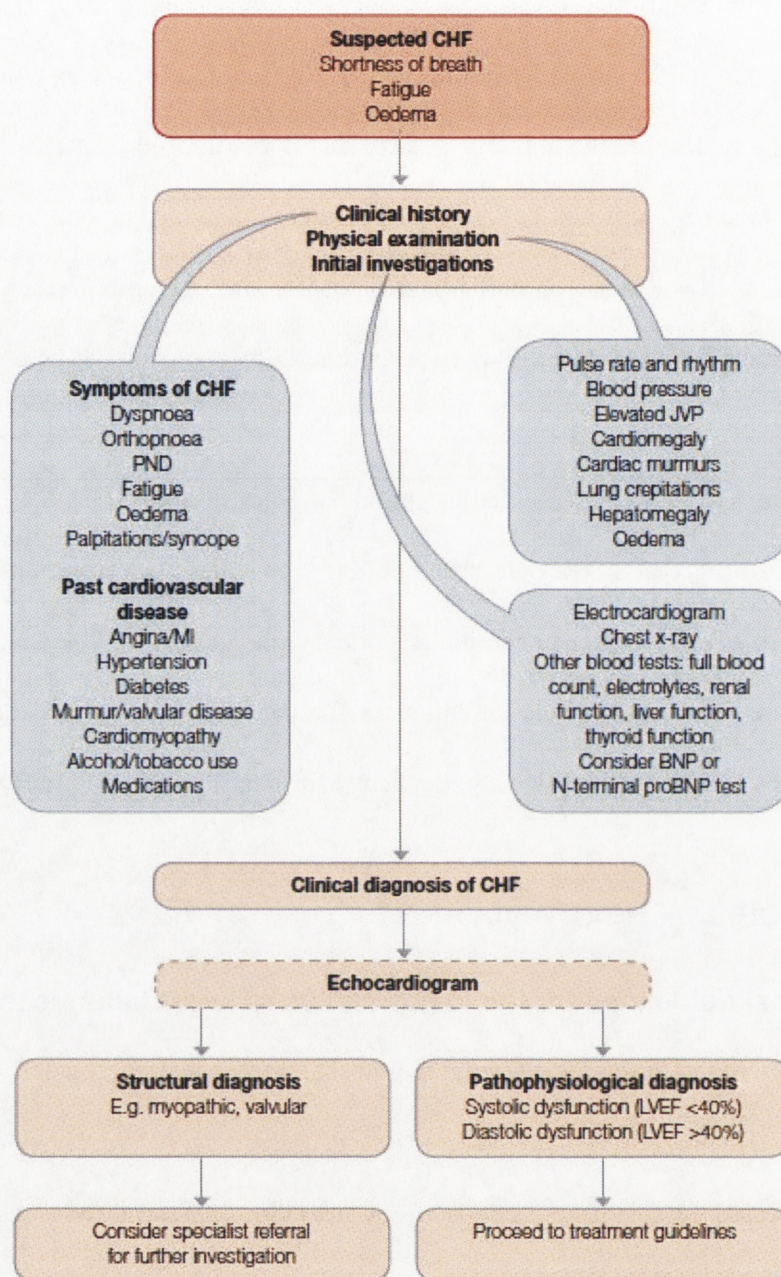


Figure 1-1 Algorithm suggested by the National Heart Foundation of Australia for the diagnosis of heart failure.

BNP = B-type natriuretic peptide; JVP = jugular venous pressure; LVEF = left-ventricular ejection fraction; MI = myocardial infarction; PND = paroxysmal nocturnal dyspnoea. From the 2006 Guidelines ⁷

1.4.2 Identification of heart failure cases in epidemiological studies

In addition to challenges in defining the syndrome of HF, accurate identification of HF cases has been limited by the absence of a gold standard diagnostic test for HF. The following methods have been used by epidemiological studies to assess the presence and severity of HF: questionnaires; physical examination; chest radiography; electrocardiogram; measures of ventricular performance; exercise testing; and biochemical detection.

All of the methods have limitations when used independently due to poor diagnostic performance, especially for individuals with mild HF. This is particularly the case when assessing an older population, in which the prevalence of co-morbid illnesses that cause symptoms and signs similar to HF is high.

The diagnostic value of symptoms, signs and chest X-ray findings for the detection of left ventricular systolic dysfunction (<40% on left ventriculography) was assessed in 1306 patients with coronary disease (mean age 51 years, 84 % male) undergoing cardiac catheterisation (Table 1-2).¹⁴ Unfortunately, the symptoms associated with the syndrome of HF are not organ specific and accurate detection of signs requires considerable clinical skills and these facts were reflected in the results of the study.

Table 1-2 Diagnostic performance of symptoms, signs and chest X-ray for LV systolic failure.

	Sensitivity (%)	Specificity (%)	+ve Predictive Value (%)
Symptoms			
Shortness of breath	66	52	23
Orthopnoea	21	81	2
Nocturnal dyspnoea	33	76	26
Oedema by history	23	80	22
Physical examination			
Tachycardia (>100/min)	7	99	6
Rales	13	91	27
Oedema on examination	10	93	3
Ventricular gallop sound (S3)	31	95	61
Neck vein distension	10	97	2
Chest X-ray			
Cardiomegaly	62	6	32

Prior to the 1990's, epidemiological studies employed either self-report or clinical scores, based on symptoms and signs to assess the presence of HF. The validity of the Framingham clinical scoring system was evaluated in a sample of 407 patients referred for assessment of left ventricular function. Both the sensitivity and specificity of the Framingham score to detect an LV ejection fraction (EF) <40% determined by the reference standard, radionuclide ventriculography, were 63%.¹⁵ Since LV diastolic function was not assessed, true cases of HF (with "normal" EF) may not have been identified by the reference standard, resulting in underestimation of the sensitivity of the Framingham score.

Mosterd applied six HF scores to a small sub-sample of participants of the Rotterdam study, a population-based prevalence study of LV dysfunction.⁸ Three of the scores were from epidemiological surveys of HF (Table 1-3), and three were derived for use in clinical trials (Walma, Boston, Gheorgiade scores). The reference standard was the cardiologist's classification (no, possible or definite HF) based on his own medical history, physical examination and echocardiographic data.

Unfortunately, due to the small number of participants (5 persons with definite HF, 17 cases with possible or definite HF), the 95 % confidence intervals were wide, limiting meaningful comparisons. The areas under the receiver operating characteristic curve (AUC) for possible and definite HF were similar for all the HF scores compared. The AUC for definite HF was a mean of 82% and for possible and definite HF was 94%.

The accuracy of clinical assessment by general practitioners has been evaluated by a number of studies.¹⁷⁻²⁰ The most rigorous of these studies was a Finnish study of patients referred by their primary care physicians with a suspected diagnosis of HF.¹⁷ The authors excluded patients with acute pulmonary oedema caused by acute myocardial ischaemia, and milder cases of HF were probably under-represented by non-referral, due to the insensitivity of clinical signs and the lack of symptoms on exertion. Using a modified Boston HF score and a physician's clinical diagnosis as the reference standard, patients were classified as having definite, possible or unlikely HF. The possibility of misclassification was minimised by subjecting patients to non-invasive tests of cardiac function, using M-Mode echocardiography

Table 1-3 Clinical criteria for heart failure in epidemiological studies

	<i>Framingham⁹</i>	<i>NHANES¹⁰</i>	<i>Men Born in 1913¹¹</i>
History			
Paroxysmal nocturnal dyspnoea	✓		✓
Orthopnoea	✓		
Dyspnoea on exertion	✓	✓	
Dyspnoea (WHO1-4)			✓
Night cough	✓		
Myocardial infarction/angina			✓
Weight loss	✓		
Swollen legs at end of the day			✓
Physical examination			
Neck vein distension	✓	✓	
Increased jugular venous pressure	✓		
Ventricular gallop sound (S3)	✓		✓
Rales	✓	✓	✓
Oedema	✓	✓	
Hepatomegaly	✓	✓	
Hepatojugular reflux	✓		
Circulation time ≥ 25 seconds	✓		
Chest X-ray			
Cardiomegaly	✓		
Acute pulmonary oedema	✓		
Pleural effusion	✓	✓	
Interstitial oedema		✓	
Alveolar changes		✓	
Redistribution		✓	
Electrocardiogram			
Tachycardia	✓	✓	
Atrial Fibrillation			✓
Pulmonary Function			
Vital Capacity	✓		

and exercise testing with respiratory gas exchange analysis, and patients were reviewed clinically 6 months after their initial assessment. Up to half of HF diagnoses made by general practitioners were incorrect. Chronic obstructive pulmonary disease, angina pectoris and obesity were the most common reasons for an incorrect diagnosis.

Following guidelines set by the European Society of Cardiology,³ the diagnosis of HF in epidemiologic studies has included an objective measure of left ventricular function, usually by echocardiography. Over the last 5-10 years, investigators have attempted to reduce the effects of misclassification by conducting epidemiologic studies with outcomes that are defined according to left ventricular (LV) structure and function. The changing epidemiology of HF in the era of cardiac imaging will be discussed in section 1.7 of the thesis.

1.4.3 Sources of data for epidemiological studies

HF surveys have not always sampled from true population bases. Other sources of data include general practice surveys; surveillance of prescriptions for HF medications, especially diuretics; national death statistics; and hospital separation data. Studies that have used these alternate sources of data produce results that are subjected to error from selection and measurement bias, limiting the internal and external validity of their results.

1.5 EPIDEMIOLOGY OF HEART FAILURE

1.5.1 Prevalence

The burden of HF in the community is considerable with a prevalence of 1-2% in the adult population.¹² However, HF is particularly prevalent in older persons with approximately 6–10% of people over the age of 65 years afflicted with the condition.¹³⁻²² Unfortunately, the prevalence of HF in the community is increasing,²³ and secular trends in population demographics and cardiovascular risk factors will continue to have a major influence on the prevalence of HF (Figure 1-2). It is projected that the global population of persons of age 60 years and over will reach 2 billion in 2050 (more than triple the number in 2000).²⁴ In the developed world, the fastest growing age group is the very old (age 80+). In addition, we are now experiencing the adverse effects of contemporary lifestyle on population health. Societal reductions in physical activity levels and increasing tendency to consume food that is high in energy and fat has resulted in increased global rates of obesity²⁵ and diabetes. By 2015, 2.3 billion people around the world will be overweight and more than 700 million will be obese according to the World Health Organization.²⁵ These factors, accompanied by recent trends in an improved survival of patients with hypertensive diseases, coronary artery disease (CAD), and HF itself, together with an increased likelihood of correct identification of HF cases by healthcare providers, are all important factors that may add to the burden of the syndrome and contribute to the observed HF 'epidemic'.²⁶ On the contrary, a factor that is likely to reduce the incidence of heart failure in the community includes the decreased incidence of myocardial infarction.²⁷

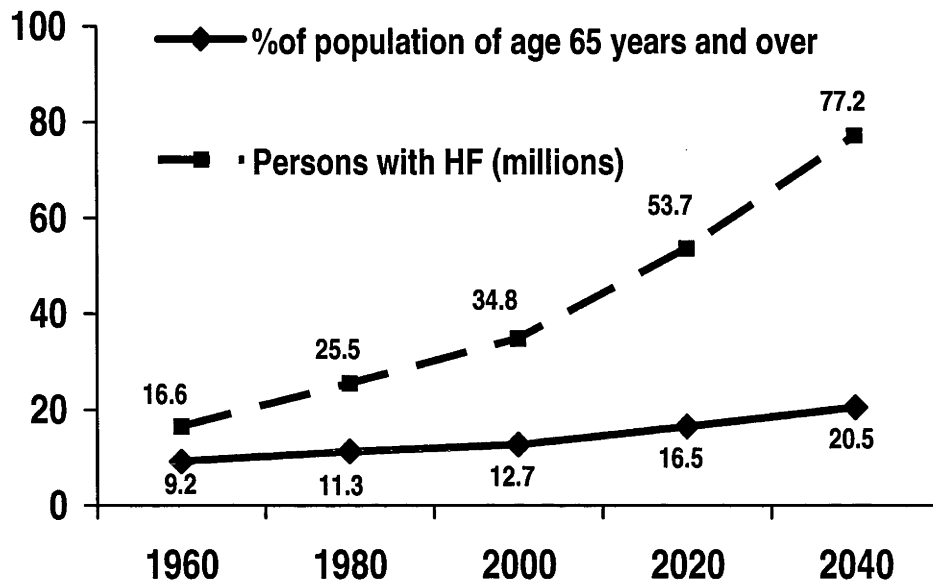


Figure 1-2 Ageing population and the increasing prevalence of heart failure.

With the ageing demographic, heart failure cases in the community have steadily increased in the past and are projected to increase exponentially in the future.

Adapted from Braunwald et al.²⁶

1.5.2 Incidence

Incident HF rates increase exponentially with age for both genders, and are approximately two times higher in men than women for each age category (Figure 1-3).²⁸ However, few studies have examined trends in HF incidence in the community.²⁹⁻³¹ Data from the Framingham Study,²⁹ which do not rely on diagnostic codes to identify HF cases and use consistent HF diagnostic criteria over the years,

are best suited for the examination of trends in the incidence of HF.

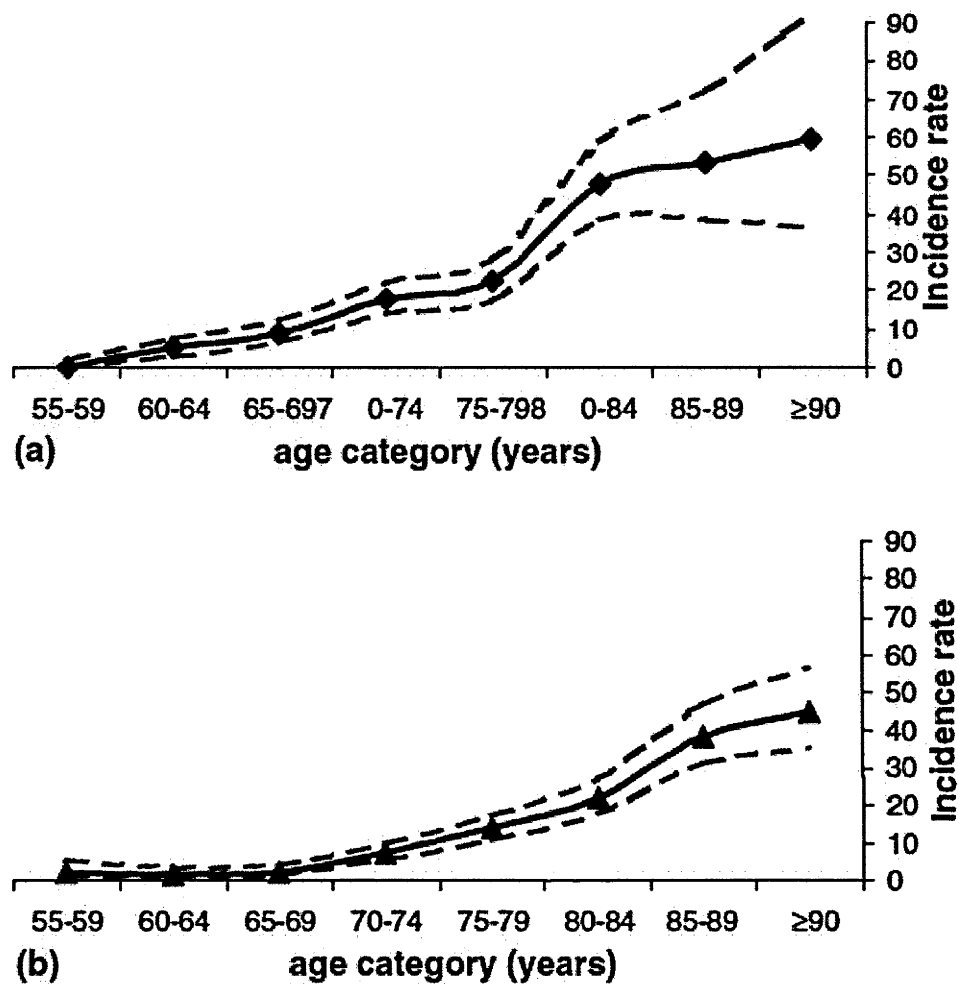


Figure 1-3 Age-specific incidence rates of heart failure.

(a) Age-specific male incidence rates (/1000 man years) and 95% confidence band.

(b) Age-specific female incidence rates (/1000 woman years) and 95% confidence band. The Rotterdam Study. Adapted from Bleumink et al. ²⁸

Despite the commonly-referenced assertion that HF is one of the “cardiovascular epidemics” to emerge in the 21st century,²⁶ studies have shown that the age-adjusted incidence of HF has remained stable over the past 20 years and thus is not a true epidemic.^{29, 30} Indeed, the Framingham Study has shown a decline in the incidence rate of HF, albeit only in women.²⁹

1.5.3 Lifetime risk

The concept of lifetime risk provides a useful framework to demonstrate the absolute cumulative risk of an individual developing a given disease during his or her remaining lifetime, and accounts for the risk of developing the disease of interest and the risk of competing causes of death. Perhaps the most robust data on HF risk originate from the Framingham Heart Study,³² although other studies have also provided estimates.²⁸ Among subjects from Framingham who were free of HF at baseline, lifetime risk of developing HF was approximately 20%. Risk varied little with age but increased according to blood pressure (BP) levels at baseline and was halved in those who developed HF without an antecedent myocardial infarction (Table 1-4).³²

Table 1-4 Remaining lifetime risk for HF and for HF in absence of antecedent MI in men and women at selected index ages

Index age, y	Men	Women
Lifetime risk for HF (95% CI)		
40	21.0 (18.7-23.2)	20.3 (18.2-22.5)
50	20.9 (18.6-23.2)	20.5 (18.3-22.6)
60	20.5 (18.1-22.9)	20.5 (18.3-22.8)
70	20.6 (17.8-23.4)	20.2 (17.8-22.6)
80	20.2 (16.1-24.2)	19.3 (16.5-22.2)
Lifetime risk for HF without MI (95% CI)		
40	11.4 (9.6-13.2)	15.4 (13.5-17.3)
50	11.6 (9.7-13.4)	15.5 (13.6-17.5)
60	11.9 (9.8-13.9)	15.8 (13.7-17.8)
70	12.6 (10.1-15.1)	16.2 (14.0-18.5)
80	13.8 (10.0-17.6)	16.1 (13.4-18.8)

All values are percentages. Adapted from Lloyd-Jones et al.³²

1.5.4 Aetiology

HF arises as a consequence of an abnormality in cardiac structure, function, rhythm, or conduction.¹² In developed countries, the commonest underlying perturbation is ventricular dysfunction that results mainly from myocardial infarction, systemic hypertension (HT), or in many cases both.²² Degenerative valve disease is becoming more common. Other common causes include alcoholic cardiomyopathy and “idiopathic” dilated cardiomyopathy, which may have a genetic basis. In less developed countries, HF may result from cardiac involvement in infectious diseases such as rheumatic valve disease, Chagas’ disease, and endomyocardial fibrosis.³³⁻³⁵

The relationship between diabetes mellitus and LV dysfunction is complex and

requires further evaluation, as does the association between atrial fibrillation and HF in patients with preserved and reduced EF.^{36, 37}

1.6 BURDEN OF HEART FAILURE ON COMMUNITY RESOURCES

1.6.1 Hospitalisations

Each year, about two individuals per thousand of the adult population are discharged from hospital with HF, accounting for approximately 5% of all medical and geriatric admissions.^{31, 38-43} Age at admission is increasing, which suggests that preventive treatments are delaying the onset of HF.^{31, 38-43} Patients discharged from hospital include those with incident HF which develops as a consequence of another cardiac event such as myocardial infarction; those presenting for the first time with decompensation of previously unidentified cardiac dysfunction; and those with established, chronic, HF who have suffered worsening of severity that requires in-patient medical management. Some of these admissions reflect the incessant natural progression of HF, whereas others are related to avoidable factors, e.g. as a result of non-adherence to treatment.⁴⁴ After years of steady rise, age-adjusted rates of HF admission appear to have reached a plateau, or perhaps even decreased.

Assessment of hospital-based records in an Australian city, Perth, showed that medical documentation of HF is poor, particularly when the condition develops as a complication of acute myocardial infarction; in patients with longstanding HF who are prone to frequent readmission for acute HF exacerbations; and among older patients.⁴⁵ It was concluded that data from hospital records was of questionable

validity for HF patients, even when compared to patients with other cardiovascular diseases such as ischaemic heart disease. Despite these limitations, analysis of hospital data to monitor general trends in hospital admissions in HF or hypertensive heart disease (principal diagnosis only) has been reported as a measure of the changing burden of disease in the community.²⁷

Over the period 1993–94 to 2000–01, rates of hospitalisation for HF or hypertensive heart disease have declined in adults of age ≥ 45 years (Figure 1-4). The decline is greatest among those aged 55–64 years, and less apparent in the very elderly (those aged ≥ 85 years).

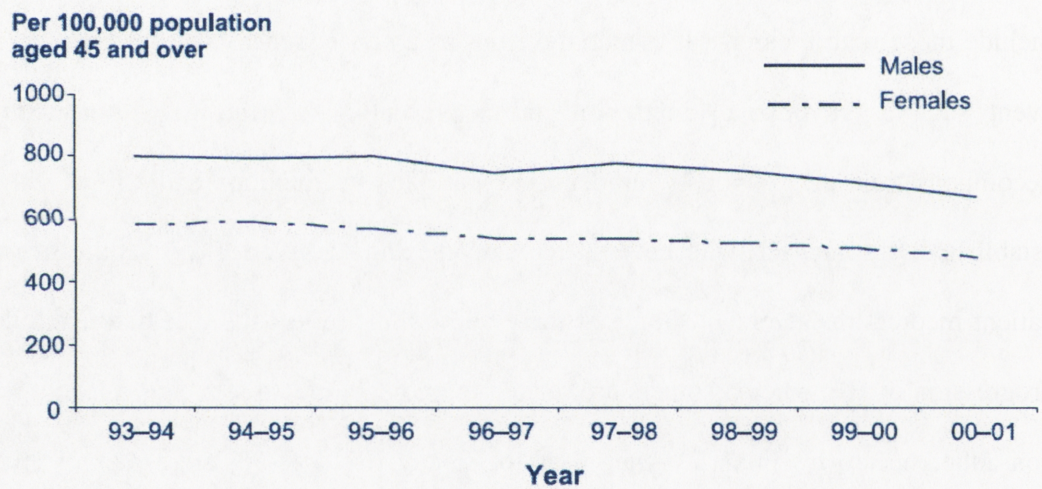


Figure 1-4 Trends in hospitalisation rates where heart failure or hypertensive heart disease was the principal diagnosis, by sex, 1993–94 to 2000–01

Adapted from Field et al.¹⁵

The average length of stay in hospital for HF patients has fallen from 9–10 days in 1993–94 to 7–8 days in 2000–01. Females are hospitalized for a longer duration than males and, not unexpectedly, older HF patients are admitted for longer (10–11 days

for those aged ≥ 85 years v 6 days for 45–54 year olds). Hospital deaths where HF or hypertensive heart disease was the principal diagnosis have also continued to decline, even more rapidly than the decline in hospital separation rates (Figure 1-5). In the period 1993–94 to 2000–01, hospital separation rates for HF fell on average by about 2% per year, whereas deaths in hospital fell by 4–5% per year reflecting a reduction in the in-hospital case-fatality rate of about 2%. This reduction suggests that in-hospital treatment for HF is improving, although the data do not account for the severity of HF cases being treated in acute care hospitals. Secular changes in admission policies over the period studied may also be influencing the trends.

Information about HF readmissions to hospital cannot be determined using the National Hospital Morbidity Database because there is no individual identifier. However, a high readmission rate is characteristic of patients with HF and is most likely contributing to the high rates of hospital admission observed in the elderly. Because of the ageing population, falls in hospital admission rates for HF in recent years (Figure 1-4) may be attributable to falls in first-ever admissions rather than falls in the readmission rate.

1.6.2 Pharmaceutical use

In Australia, national data on the use of subsidised prescription drugs are available from various data sources including the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme. However, these data are limited by their lack of specificity as they do not include information about the condition for which a drug is being prescribed. For instance, many of the vasoactive medications

used to treat HF can also be prescribed for more common conditions such as HT. Non-subsidised medications are not represented in these data sources.

Using data from primary care practices, it was shown that patients with HF were prescribed more medications than other patients of the same age.⁴⁶ As anticipated and according to consensus guidelines, HF patients were often on a combination of medications including diuretics, digitalis and related drugs, potassium supplements, ACE inhibitors, nitrates and aspirin. Since that audit, the use of β -blockers has increased with the emerging evidence for benefits in patients with HF-rEF.

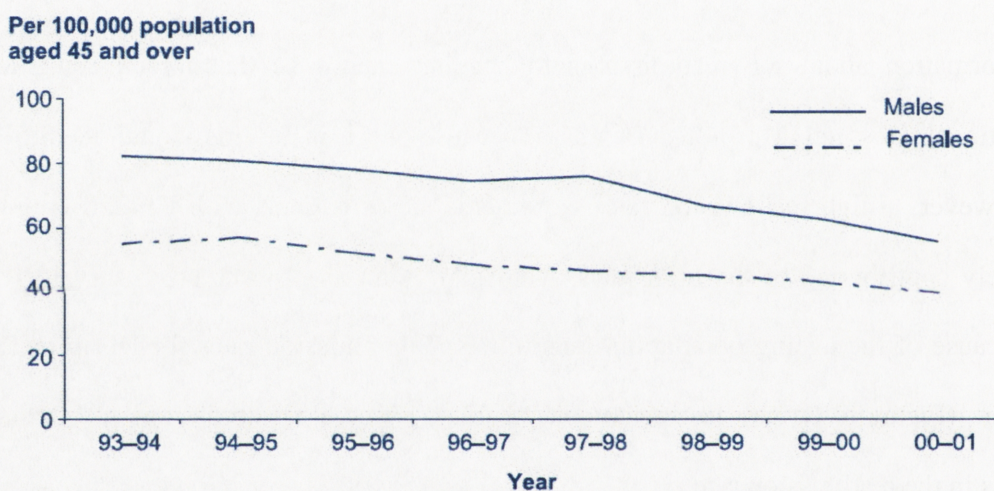


Figure 1-5 Trends in in-hospital death rates where heart failure or hypertensive heart disease was the principal diagnosis, by sex, 1993–94 to 2000–01.

From Field et al.²⁷

1.6.3 Mortality

Most reports on the trends in survival of patients with HF have shown secular improvement in age-adjusted death rates attributed to HF.^{29, 30, 47} In Australia, the decline in rates of HF deaths during the period 1997–2003 was accompanied by little

change in the proportion of deaths from HF relative to competing causes (deaths from other cardiovascular diseases), suggesting that the decline in mortality from HF was likely to reflect a real change in the epidemiology of HF.⁴⁸ HF and hypertensive heart disease accounted for 3,205 deaths in 2001 among people aged ≥ 45 years with nearly 90% of these deaths occurring in people aged ≥ 75 years. Between 1993- 2001, mortality rates declined for both sexes (Figure 1-6). The decline in death rates was lowest among 55–64 year olds, whereas this age group experienced the greatest fall in hospitalisation rates over a similar period of time. Death rates were similar between men and women (41 deaths per 100,000 v 38 deaths per 100,000, respectively). This contrasts with the disparity between hospitalisation rates and in-hospital death rates, where male death rates are much higher than those for females (Figures 1-4 and 1-5). The observation that women are less likely to be readmitted to hospital because of their role as carers in the community may be contributing to the gender differences.⁴⁹ It may also reflect the under-diagnosis of HF in women.

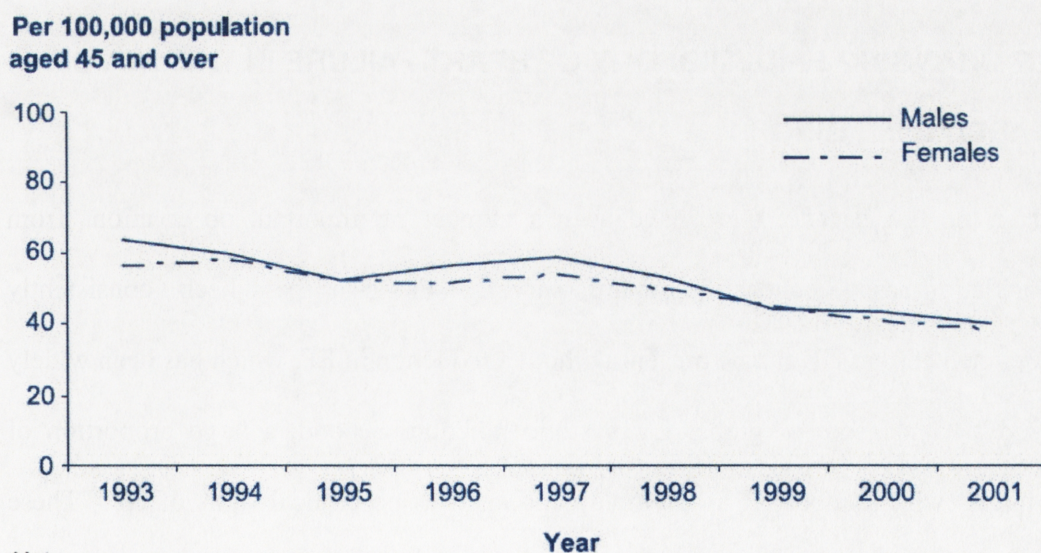


Figure 1-6 Trends in death rates where heart failure or hypertensive heart disease was the underlying cause, by sex, 1993 to 2001.

From Field et al.²⁷

1.6.4 Economic costs

National data on the cost of various diseases are limited to their “direct” costs, including hospital in-patient services; outpatient services; pharmaceuticals; GP and specialist consultations; allied health services; pathology tests; screening and diagnostic imaging services; and nursing homes. Disease costs that are not captured are related to community health services; public health programs; ambulance services; and medical aids and appliances. In 1993–94, the direct health care costs for HF were estimated to be \$411 million, which equates to 10% of the total costs attributable to cardiovascular disease. HF costs were ranked fourth behind coronary heart disease (23%), HT (21%) and stroke (16%).⁵⁰

1.7 CHANGING EPIDEMIOLOGY OF HEART FAILURE IN THE ERA OF CARDIAC IMAGING

Over the last decade, there have been a number of important observations from population-based echocardiographic surveys. First, it has been consistently documented that HF can be present without a reduction in EF, which has been widely used as a measure of global LV systolic function. Second, a large proportion of subjects with reduced EF is asymptomatic and has no clinical signs of HF. These observations have stimulated interest in the pathophysiology and natural history of HF.

1.7.1 Heart failure with normal ejection fraction (HF-NEF)

Comparisons of studies examining the epidemiology of HF with normal EF (HF-NEF) have been limited by the lack of clear consensus regarding a definition of the syndrome.^{51, 52} Thus there are differences in study setting and patient populations (ambulatory versus hospital populations), and major differences in the methods used to diagnose the presence of clinical HF and to confirm preservation of LV systolic function.^{51, 52} Despite these limitations, studies have provided consistent results.

Most studies have reported that one third to one half of patients presenting with HF in a community setting have normal or near normal LV systolic function as defined by a EF of greater than 40-50%.^{20, 53-56} A review by Hogg et al.⁵⁴ reported the prevalence rates of HF in European and North American studies according to preserved or impaired left ventricular systolic function (Figure 1-7). Differences in prevalence rates of total HF relate predominantly to differences in mean age of the populations, but also to the factors discussed above. Across all of these HF studies, the mean proportion of patients with preserved systolic function was 56%.⁵⁴

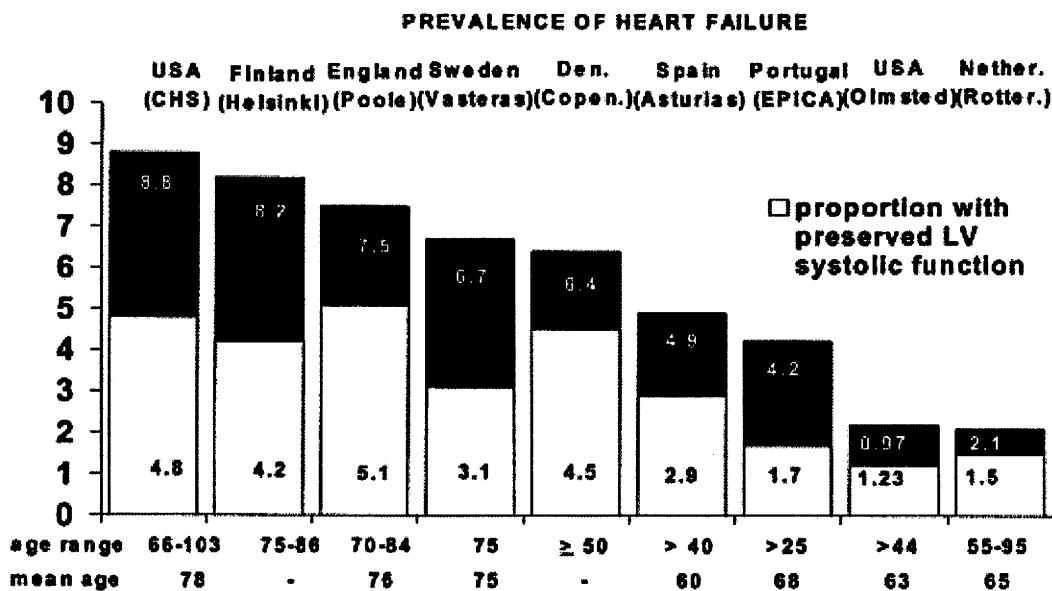


Figure 1-7 Prevalence of heart failure in European and North American studies according to preserved or impaired left ventricular systolic function

From Hogg K et al.⁵⁴

Other consistent findings are that the syndrome is relatively more common in women,⁵⁶ and is strongly associated with HT.⁵⁷ Diabetes and CAD are also relatively common in these patients. However, one of the most important risk factors for HF-NEF is advanced age, consequent to age-related structural changes that occur in the ventricle, principally myocardial fibrosis. In patients >65 years of age, the majority of HF patients will have preserved LV systolic function, a finding even more dominant in elderly women.⁵⁸

Despite repeated confirmation that HF-NEF is more common in women than men, population studies assessing the prevalence of DD have found DD to be either gender neutral or more common in men.^{20, 59} The reasons for this paradox are not obvious, but this finding suggests that gender differences may exist in the pathophysiological

pathways that lead from DD to decompensated HF, and that mechanisms other than DD are involved.

1.7.1.1.1 Conceptual issues regarding the definition of HF-NEF

A fundamental concept in approaching a description of HF-NEF relates to whether one embraces an “inclusive” or “exclusive” definition of the syndrome. While an exclusive definition requires only documentation of normal EF be present in the setting of clinical HF, an inclusive definition further requires the demonstration of abnormal diastolic function, which is causally linked to the clinical HF. While an inclusive definition has the advantage of increasing the specificity of the diagnosis, it obviously requires assessment of diastolic function, which is often a very difficult task. Indeed, assessment of diastolic function has historically been perceived to be too complex for non-invasive methods, and the majority of investigators have therefore defined HF-NEF as a diagnosis of exclusion. When assessment of diastolic function is omitted, the exclusive definition assumes the clinical syndrome to be secondary to DD; however other possibilities also exist, including for example valvular dysfunction, intermittent ischaemia or intermittent atrial fibrillation.

The second fundamental concept to consider in establishing a diagnosis of HF is that of acute versus chronic HF. Acute episodes are characterised by rapid onset ("flash") pulmonary oedema and have unequivocal physical signs and chest X-ray evidence of pulmonary venous congestion.^{60, 61} Most of the epidemiological data which follows refers to patients who at some stage have had decompensated HF, usually requiring hospitalisation. In contrast, patients with chronic HF-NEF are poorly characterised, although they potentially comprise a significant proportion of the hypertensive

population who report exertional breathlessness. These ambulatory patients are relatively asymptomatic at rest, but complain of exercise intolerance which is likely due to a combination of high filling pressures during exercise, as well as reduced stroke volume. Whilst the clinical presentations of these two syndromes are markedly different, recent evidence suggests that they likely represent two ends of the spectrum of the same phenomenon. Thus, the vast majority of patients who are admitted to hospital with acute HF-NEF report preceding chronic symptoms consistent with New York Heart Association (NYHA) class II-IV.⁶² It is important to note that as patients with chronic HF-NEF may be well-compensated and asymptomatic at rest, and clinical signs of HF are often absent. In this syndrome therefore, it is even more important to require that the diagnosis of HF-NEF includes confirmation of DD

1.7.1.1.2 Current definitions of HF-NEF

There are two groups who have published guidelines for diagnosing HF-NEF. Vasan et al have suggested that, in order to achieve a diagnosis of “definite” HF-NEF, patients are required to have clinical signs of decompensated HF which satisfy Framingham criteria; have a normal EF documented within 72 hours of the HF episode, and have abnormal diastology demonstrated at left heart catheterization.⁶³ If the first two criteria are satisfied but invasive assessment is not performed, the patient is deemed to have only “probable” HF-NEF. As cardiac catheterization is generally not indicated in this condition, very few patients would receive a definite diagnosis of HF-NEF under these guidelines, making them clinically impractical.

The latest criteria proposed by the European Society of Cardiology (ESC) for the diagnosis of HF-NEF include all of the following⁶⁴: (a) the presence of signs or symptoms of HF, (b) the presence of normal or mildly abnormal EF, and (c) evidence of DD (by cardiac catheterisation, Doppler echocardiography, and the measurement of plasma levels of natriuretic peptides). However, these criteria do not take into account mechanisms, other than DD, which also cause HF in the presence of a normal EF. In addition, ESC guidelines do not address the lack of sensitivity in patients who have increased filling pressures only during exercise, but not at rest.

In contrast, the American College of Cardiology / American Heart Association (ACC/AHA) Heart Failure Guidelines 2001 provide no specific criteria for the diagnosis of HF-NEF. Instead, the taskforce states that “it is difficult to be precise about the diagnosis of DD”, and support a diagnosis of exclusion, based on symptoms and signs of HF in patients with a normal EF and no valvular abnormalities. Somewhat surprisingly, these recommendations were not modified in the recently updated guidelines.⁵

1.7.1.1.3 Prognosis of HF-NEF

In a community cohort from the Framingham Heart study followed for a median of 6.2 years, patients with HF-NEF (EF \geq 50%) had a lower mortality compared patients with impaired EF. However, the former group still had a fourfold mortality risk compared with control subjects who were free of HF.⁵⁶ In one of the few studies of incident cases of HF, patients receiving a new diagnosis of HF over a 1 yr period had

a mean age of 77 years.⁵⁵ Forty-three percent of these patients had an EF $\geq 50\%$, and after adjusting for age, sex, functional class, and the presence of coronary disease, survival was not significantly different between patients with normal and those with reduced systolic function (Figure 1-8).⁵⁵ Similar findings were reported in a contemporary study of Olmsted County residents.⁶⁵

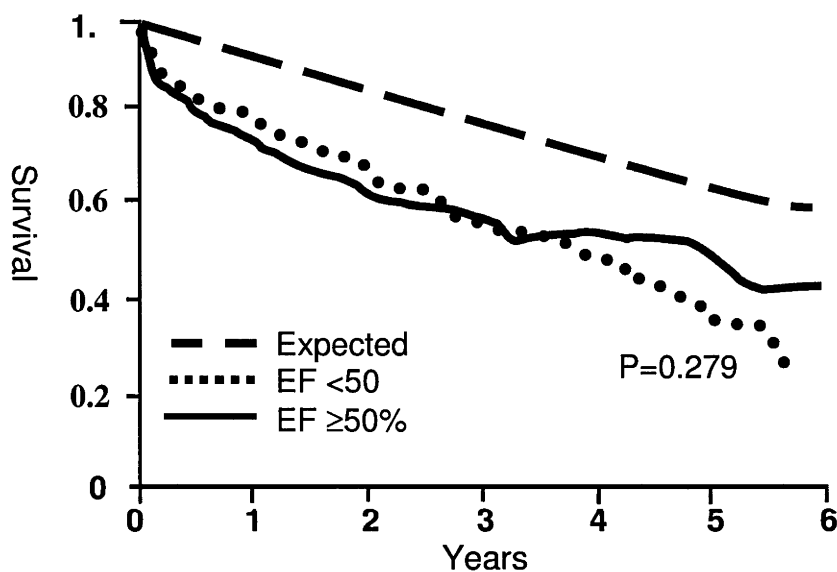


Figure 1-8 Survival in heart failure patients with preserved versus impaired systolic function: Historical evidence.

Modified from Senni et al.⁵⁵ EF = ejection fraction.

1.7.1.1.4 Medical therapy and trends in survival for HF-NEF patients

Unfortunately, there is very little evidence on which to recommend medical therapy for patients with HF-NEF. The results of recent clinical trials on medical therapy for HF-NEF have been disappointing (Table 1-5). In general, the empirical management of HF-NEF has 2 objectives: (i) treatment of the presenting syndrome of HF,

including the therapy directed at venous congestion and precipitating factors such as atrial fibrillation with a poorly controlled ventricular response; (ii) treatment directed at risk factors for DD such as HT.^{5,6}

Table 1-5 Randomised controlled trials for the treatment of heart failure in patients with normal ejection fraction

Agent	Study outcomes	Result
Candesartan ⁶⁶	CV death, HF hospitalization	No effect
Nebivolol ⁶⁷	Death, CV hospitalization	No effect*
Digoxin ⁶⁸	HF death, HF hospitalization	No effect
Perindopril ⁶⁹	Death, HF hospitalization	No effect
Irbesartan ⁷⁰	Death, CV hospitalization	No effect
Spironolactone	CV death, HF hospitalization	Due to report 2010

*inadequately powered to show separate effect in EF>35%

At present, there are ongoing clinical trials in HF-NEF that aim to test the efficacy of aldosterone antagonists (TOPCAT study), nesiritide, beta-blockers (Japanese diastolic heart failure trial) and sildenafil (RELAX trial).

The rate of morbidity and mortality of patients with HF-rEF has gradually improved during the past 2 decades, reflecting the impact of several evidence-based interventions that have been incorporated into the care of patients with HF-rEF (Figure 1-9).

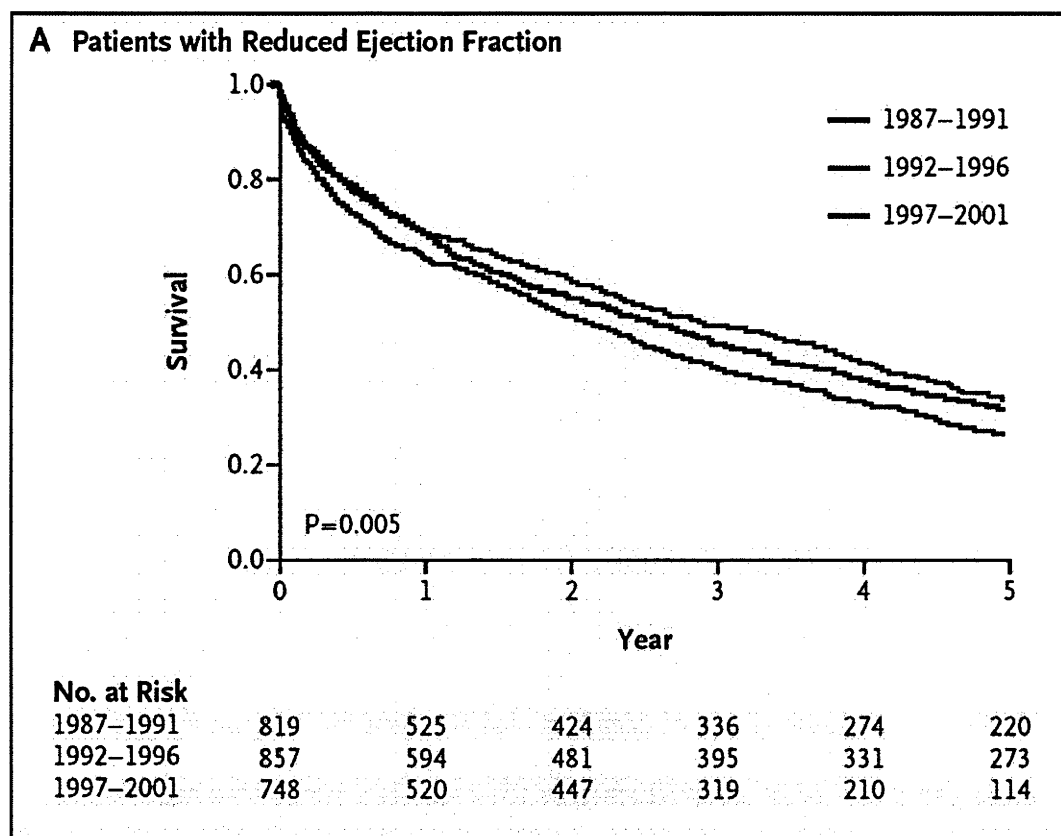


Figure 1-9 Trends in survival in heart failure patients with reduced ejection fraction: 1987-2001.

From Owan et al.⁶⁵

In contrast, the prognosis of patients with HF-NEF has remained steadfastly unchanged during the same time period (Figure 1-10), reflecting the dearth of therapeutic interventions that have been evaluated in HF-NEF, and the failure of these therapies to show any benefit on survival in patients with this syndrome. Thus, there is an urgent need to develop novel and efficacious strategies for the treatment of HF-NEF, particularly ones that specifically target the pathophysiologic mechanisms that underlie HF-NEF.

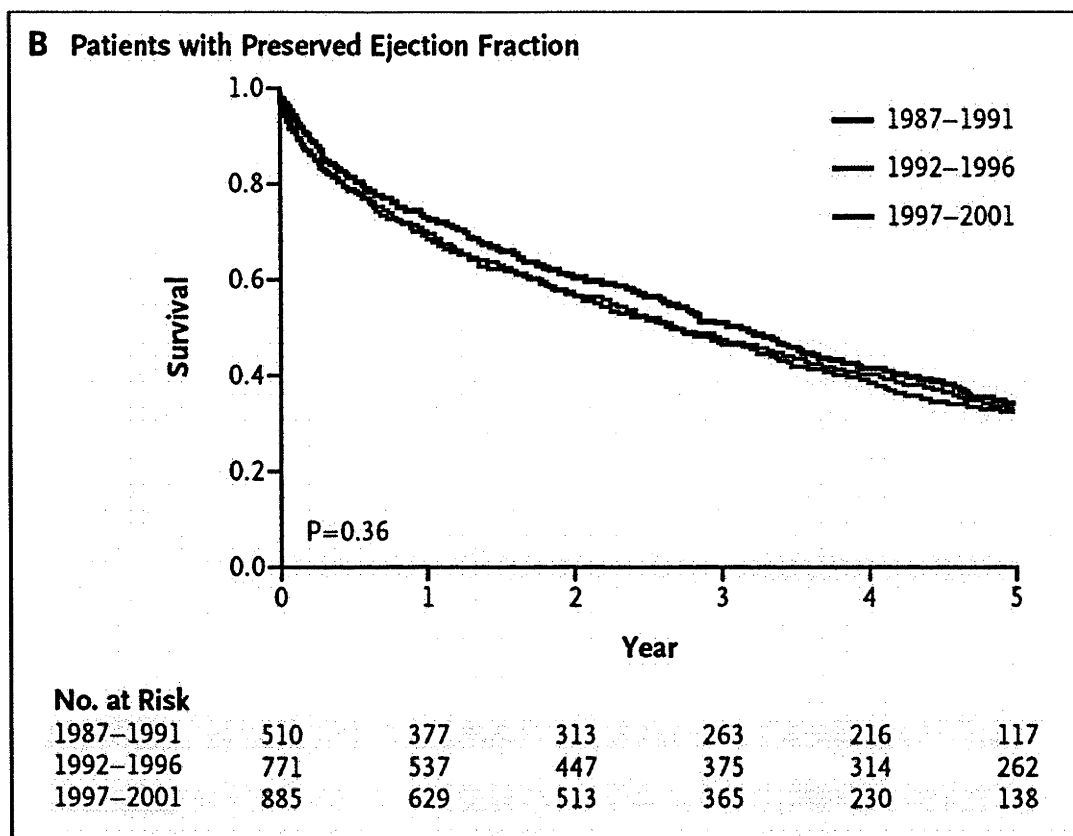


Figure 1-10 Trends in survival in heart failure patients with preserved ejection fraction: 1987-2001.

From Owan et al.⁶⁵

1.7.2 Role of diastolic dysfunction in the aetiology of HF-NEF

In considering the aetiology of HF-NEF, the obvious question to ask is whether HF-NEF is actually caused by DD. As discussed, definitions of exclusion have assumed DD to not only be present, but to be causative. While early evidence did indeed support the view that the key problem in HF-NEF is an abnormal diastolic pressure-volume relationship,⁷¹ it is only quite recently that this hypothesis has been actively investigated.

In 2001, Zile et al reported a study of a highly selected group of 63 patients with clinically defined HF and normal EF who were already scheduled for left heart catheterization and a detailed echo-Doppler study.⁷² All patients had LV hypertrophy or concentric LV remodelling. The results showed that LV end-diastolic pressure was elevated in 92% of patients. At least one index of diastolic function was abnormal in every patient, leading the authors to conclude that the diagnosis of HF-NEF can be reliably made clinically.⁷²

In the same year, Gandhi et al reported a study of 38 patients who presented with acute pulmonary oedema and HT (mean systolic BP approximately 200 mmHg).⁶¹ Echocardiography was performed during the acute presentation and again after treatment demonstrated a similar EF (approximately 50%) at both studies. No patient had severe mitral regurgitation during the acute episode. These authors suggested that the acute pulmonary oedema was therefore due to exacerbation of DD by HT rather than transient systolic dysfunction.

More recently, Zile et al published a second report with more detailed haemodynamic information on 47 patients from the original study who had undergone micromanometer studies at left heart catheterization.⁷³ Compared with healthy controls, patients with HF-NEF had longer time constant of LV relaxation, higher minimal LV pressure and higher LVEDP, despite lower diastolic volumes. They also had increased LV chamber stiffness illustrated by an upward and leftward shift in pressure-volume curves (Figure 1-11). Thus patients with HF and normal EF were demonstrated to have impaired active LV relaxation and increased passive LV

stiffness. Most importantly, the authors believed that these abnormalities were sufficient to explain the patients' elevated diastolic pressures and clinical HF.⁷³

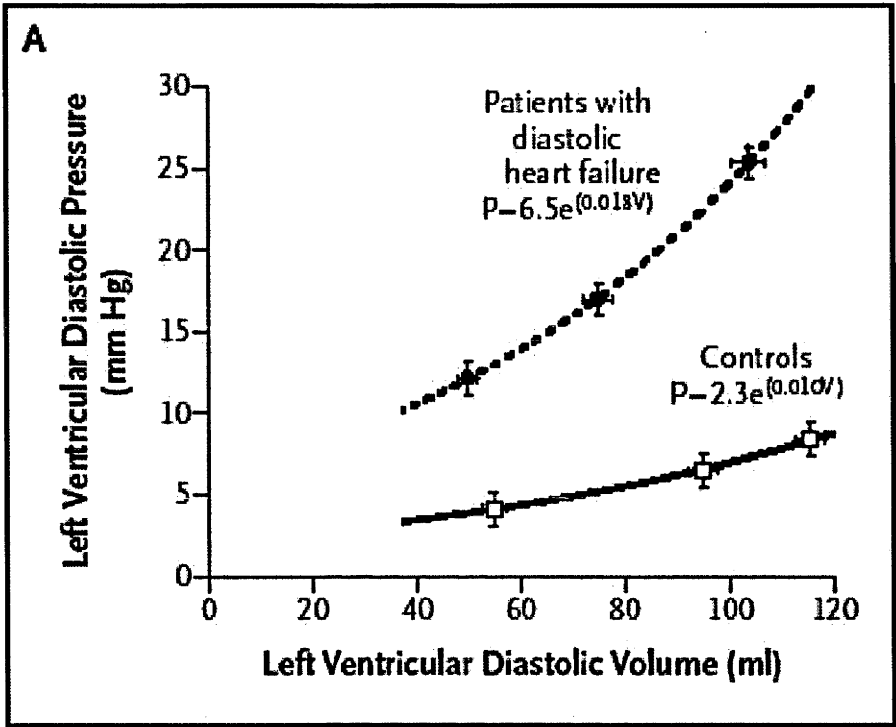


Figure 1-11 End-diastolic pressure volume curves in patients with diastolic heart failure versus controls.

From Zile et al.⁷³

Despite the careful and detailed methodology of this invasive study, the highly selected nature of the patient group limits extrapolation to the large clinical population of patients presenting with HF-NEF. Two studies of unselected patients with suspected HF-NEF have addressed this issue. Cahill et al evaluated the incidence of DD in a group of consecutive patients hospitalised with HF who had normal EF and no significant valvular dysfunction, and found that less than half of such patients had isolated DD.⁷⁴ Similarly, among consecutive patients with

suspected HF-NEF function referred for echocardiography, Petrie et al found very poor concordance among different published criteria for the diagnosis of DD.⁷⁵

Burkhoff et al compared end-diastolic pressure-volume relations in patients with HF-NEF and normal controls from several studies and found variable results (Figure 1-12).⁷⁶ The authors concluded that there is no consistent abnormality of diastolic properties that can explain the occurrence of HF with normal systolic function.

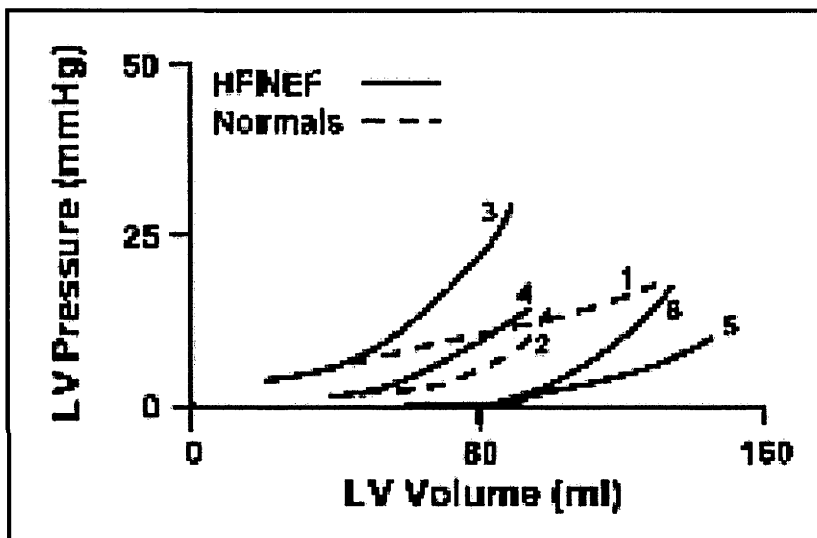


Figure 1-12 End-diastolic pressure-volume relations in different populations of patients with heart failure and normal left ventricular ejection fraction.

Curves of patients with HFNEF may be shifted to the left (curve 3), shifted to the right (curves 5 and 6), or may not be significantly different (curve 4) than those of normal patients (curves 1 and 2). HFNEF = heart failure with normal ejection fraction. From Burkhoff et al.⁷⁶

The reasons for these discrepant results are not obvious, but likely relate to differences in patient selection leading to heterogeneity of patient characteristics in

different studies of HF and preserved LV systolic function. However, this explanation is not the full story as the clinical syndrome of “decompensated” HF is associated with other pathophysiological factors. LV diastolic function is not necessarily the sole or even dominant factor in HF-NEF. A low cardiac output is one of the fundamental abnormalities of HF of any cause, whether it be predominantly systolic or diastolic HF.^{77, 78} Furthermore, a strong theoretical argument can be made to relate low cardiac output to the known pathophysiological characteristics of HF-NEF.⁷⁷ In addition, neurohormonal activation, which is associated with HT and increased venous tone is prominent in HF-NEF, and not dissimilar to that seen in systolic HF.⁷⁹ As a consequence of reduced cardiac output and neuro-humoral activation, decompensated HF-NEF, like HF-rEF, is characterised by increased sodium and water retention. Finally, increased arterial stiffness is likely to be important in the pathophysiology of HF-NEF;⁸⁰ this subject will be discussed in detail later in this chapter.

Despite the likely importance of all of these factors, they do not necessarily cause HF in patients with normal LV structure and function. When considering the totality of evidence, therefore, one can conclude that decompensated HF-NEF occurs through the interaction of the underlying substrate of DD with the exacerbating peripheral factors described above.

1.7.2.1.1 Ventricular-arterial interaction in HF-NEF

In addition to its direct haemodynamic load, HT is associated with increased aortic stiffness which may contribute further to hypertrophic LV remodelling. Increased pulsed wave velocity through stiffened arteries results in the early return of reflected

pressure waves before systole is completed thereby increasing LV afterload, which of itself can directly impair LV relaxation.⁸¹ Aortic stiffening also reduces central diastolic pressure resulting in decreased coronary perfusion which may exacerbate subendocardial ischaemia in the setting of LV hypertrophy.⁸²

Arterial stiffening is also associated with increased ventricular stiffness which in combination lead to markedly reduced cardiovascular reserve that is particularly characteristic of elderly hypertensives.^{83, 84} Patients with HF and preserved systolic function are also characterised by increased aortic and ventricular stiffness, resulting in impaired ventricular-arterial interaction which may be important to the pathophysiology of decompensated HF-NEF.⁸⁰ In addition, increased arterial stiffness appears to be mechanistically related to the severe exercise intolerance in stable patients with HF-NEF.⁸⁵

Recent studies have also shown that age-related increases in ventricular and arterial stiffness occur in tandem and may be more pronounced in women,^{83, 86} which may explain the predilection of HF-NEF in older women. It has been proposed that these age-related alterations in vascular–ventricular coupling may contribute to exercise intolerance and could predispose to the development of DD⁸⁷ and HF-NEF.^{80, 88}

Despite the emerging evidence for a key role of arterial function in HF-NEF, few studies have assessed the relationship of arterial stiffness to echocardiographic parameters of LV diastolic function.

1.7.3 Detectable preclinical phase of disease

The confirmation of a stage of preclinical LV dysfunction in echocardiographic surveys has provided greater opportunity to delineate the natural history of HF. The information from these studies has emerged in tandem with a better understanding of the physiology of cardiac function and technological advances in non-invasive cardiac imaging.

1.8 UNDERSTANDING THE NATURAL HISTORY OF DISEASE

1.8.1 Asymptomatic left ventricular systolic dysfunction

For many years, clinicians have been aware that a reduced EF without increased LV filling pressures can be documented in patients without symptoms/signs of HF. Over the last decade, their anecdotal findings have been confirmed using population-based echocardiographic surveys that have consistently found that a large proportion of subjects with reduced EF is asymptomatic and has no clinical signs of HF.

1.8.1.1.1 Asymptomatic LV systolic dysfunction: Epidemiology

There is now a large body of evidence to support the assertion a large proportion of subjects with reduced EF is asymptomatic and has no clinical signs of HF (Table 1-6).

Table 1-6 Prevalence of asymptomatic left ventricular systolic dysfunction

Study (Reference)	Country	Participants	Mean Age	Men	LVSD Criteria	Prevalence of LVSD	Prevalence of LVSD without CHF†
		n	y	%		%	
EF > 0.40, or equivalent							
Strong Heart Study (26)	United States	3184	58	37	EF ≤ 0.54	14.0	12.5
HyperGEN Study (27)	United States	2086	55	38	EF ≤ 0.54	14.0	12.9
Davies et al. (28)	England	3960	61	50	EF ≤ 0.50	5.3	3.3
MONICA project (Augsburg) (29)	Germany	1566	50	48	EF < 0.48	2.7	1.1‡
Hedberg et al. (30)	Sweden	412	75	50	WMI < 1.7	6.8	3.2
Nielsen et al. (31)	Denmark	126	70	55	WMI ≤ 1.5 or FS < 0.26	2.9	1.0
Rotterdam Study (32)	Netherlands	2267	66	45	FS ≤ 0.25	3.7	2.9§
Helsinki Ageing Study (33)	Finland	501	—¶	27	FS < 0.25	10.8	8.6
EF ≤ 0.40							
Strong Heart Study (26)	United States	3184	58	37	EF < 0.40	2.9	2.1
HyperGEN Study (27)	United States	2086	55	38	EF < 0.40	4.0	3.4
Davies et al. (28)	England	3960	61	50	EF < 0.40	1.8	0.9
MONICA project (Glasgow) (34)	Scotland	1467	50	48	EF ≤ 0.35	7.7	5.9
MONICA project (Glasgow) (34)	Scotland	1467	50	48	EF ≤ 0.30	2.9	1.4
Qualitatively "reduced" EF							
Cardiovascular Health Study (35)	United States	5532	73	42	Qualitative¶	3.5	2.5
Morgan et al. (36)	England	817	76	46	Qualitative	7.5	3.9

From Wang et al.⁸⁹

Given the potential expense of widespread echocardiographic screening, there is interest in targeting subgroups at high risk for LV systolic dysfunction (LVSD) who could be efficiently screened.^{90, 91} Four studies reported the prevalence of asymptomatic LVSD in specific subgroups.⁹¹⁻⁹⁴ The prevalence of asymptomatic LVSD was twofold to eightfold higher in men than in women and higher in elderly persons. Indeed, the prevalence of asymptomatic LVSD in women was low, ranging from 0.2% to 1.1% in community-based studies.^{91, 93, 94} When clinical features were considered, the prevalence was highest among individuals with known coronary heart disease, ranging from 4.8% to 8.5%.^{91, 93, 94} Only three studies enrolled an appreciable number of non-White participants.^{92, 94, 95} The Strong Heart Study reported a high prevalence of LVSD in a community-based study of Native American participants.⁹⁵ In the Hypertension Genetic Epidemiology Network Study and the Cardiovascular Health Study, LVSD prevalence rates were slightly higher in black participants than in White participants.^{92, 94}

1.8.1.1.2 Asymptomatic LV systolic dysfunction: Prognosis

In community-based observational studies, asymptomatic LVSD was associated with increased cardiovascular mortality⁹⁴; all-cause mortality^{94, 96}; and nonfatal cardiovascular events, such as myocardial infarction and stroke.^{94, 97} Little is known about the rate of progression from asymptomatic LVSD to overt HF in the community. In an earlier investigation from the Cardiovascular Health Study, Aurigemma and colleagues⁹⁸ reported an annual HF incidence of 3% for individuals with LVSD, but this estimate was restricted to individuals without coronary heart disease.

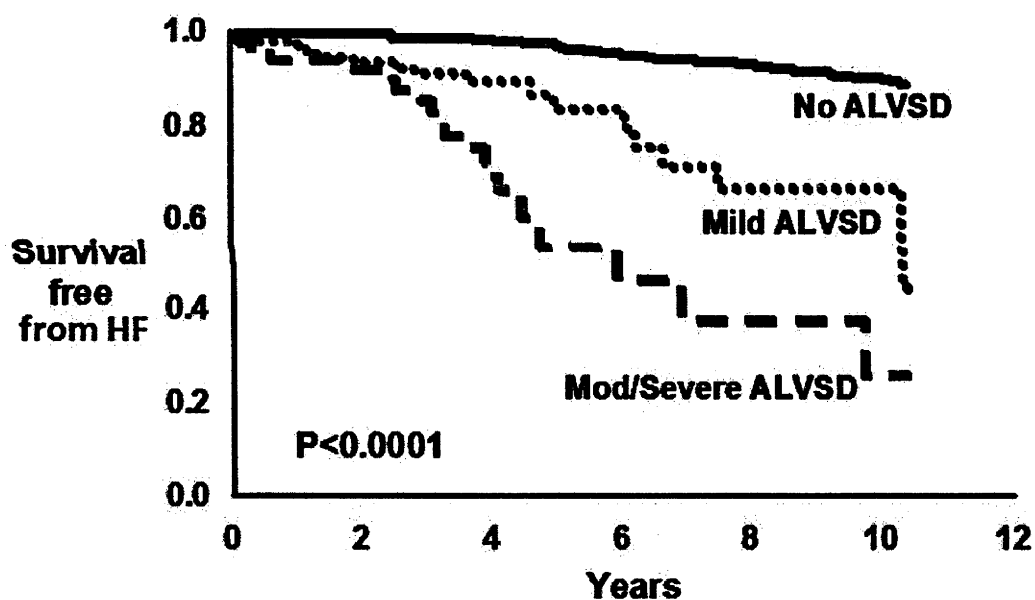


Figure 1-13 Kaplan-Meier survival curves showing freedom from heart failure for subjects with asymptomatic left ventricular systolic dysfunction.

Referent group consists of subjects with normal left ventricular systolic function (EF =50%). Mild ALVSD indicates mild asymptomatic left ventricular systolic

*dysfunction (EF 40% to 50%); Mod/Severe ALVSD, moderate-to-severe asymptomatic left ventricular systolic dysfunction (EF<40%). From Wang et al.*⁸⁹

In the placebo groups of five randomized, controlled trials that included more than 3500 participants with asymptomatic LVSD, average annual HF rates ranged from 4.9% to 20.0% (Figure 1-13), and average annual mortality rates ranged from 5.1% to 10.5% (8, 9, 42–44).⁹⁹⁻¹⁰³ These mortality rates are intermediate between those of persons with previous myocardial infarction and preserved systolic function and those of patients with systolic HF.^{99, 104} (Figure 1-14)

Although randomized trials provide the largest source of data on prognosis of patients with asymptomatic LVSD, extrapolating these data to individuals in the community is problematic for several reasons. First, with the exception of SOLVD, all other trials enrolled patients in the setting of a recent myocardial infarction; even in SOLVD, nearly 80% of participants had previous myocardial infarction.⁹⁹ Second, many participants enrolled in trials are not truly asymptomatic but may have NYHA class II symptoms or previous HF. Third, most trials excluded people with mild LVSD (EF 40-50%), even though most people identified in community-based studies fall into this category. Finally, trial participants were younger than typical individuals with LVSD in the community.

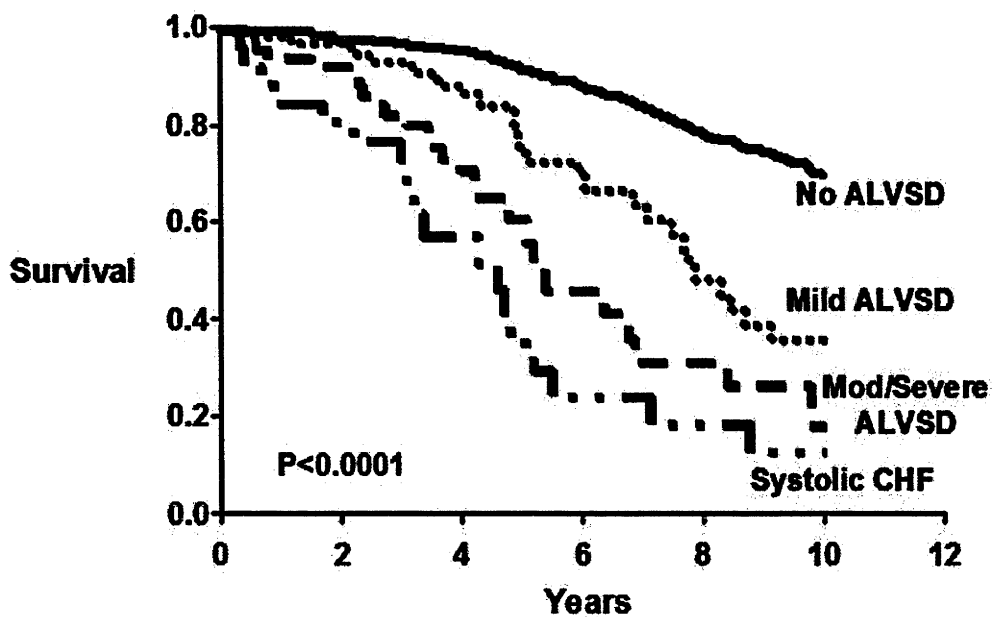


Figure 1-14 Kaplan-Meier survival curves showing prognostic significance of asymptomatic left ventricular systolic dysfunction.

Referent group consists of subjects with normal left ventricular systolic function (EF=50%) and no history of HF. Mild ALVSD indicates mild asymptomatic left ventricular systolic dysfunction (EF 40% to 50%); Mod/Severe ALVSD, moderate-to-severe asymptomatic left ventricular systolic dysfunction (EF<40%); Systolic HF, congestive heart failure with EF<50%. From Wang et al.⁸⁹

1.8.1.1.3 Asymptomatic LV systolic dysfunction: Treatment

Only ACE inhibitors have been shown to improve outcomes in patients with asymptomatic LVSD. In the SOLVD Prevention trial,⁹⁹ treatment with enalapril was associated with a 37% reduction in HF and a nonsignificant reduction in mortality. The SAVE trial¹⁰⁰ demonstrated reductions in both incidence of HF requiring hospitalization (22%) and mortality (19%) associated with captopril treatment in patients with asymptomatic LVSD after myocardial infarction. Accordingly, both the

ACC/AHA and the European Society of Cardiology recommend treatment with ACE inhibitors in patients with HF-rEF with or without previous myocardial infarction.^{4,}

¹⁰⁵ However, most individuals with LVSD in the community who would be identified by screening would not have been eligible for the SOLVD or SAVE trials. Thus, it remains unclear whether they would benefit similarly from treatment.

1.8.2 Asymptomatic left ventricular diastolic dysfunction

Since the commencement of the Canberra Heart Study, evidence has emerged that confirms that “isolated” DD is prognostically important, even in the absence of clinical HF. Redfield et al examined 2,042 randomly selected subjects of age 45 years and over.²⁰ HF, which was validated using Framingham criteria, was documented in 2.2% of the population. Diastolic function was comprehensively assessed with Doppler echocardiography, including the measurement of transmitral and pulmonary venous flow and mitral annular velocity using TDI. Diastolic function was categorised as normal or impaired to a mild, moderate or severe degree. Subjects were passively followed up for a median of 3.5 years. The authors found that moderate or severe DD in the setting of normal LV systolic function was common, being present in 5.6% of the population. These degrees of DD were associated with a hazard ratio for all-cause mortality of 10 in comparison with subjects who had normal diastolic function even in the absence of clinical HF, which was recognised in less than half of such patients. Somewhat surprisingly, even mild DD conferred a hazard ratio of 8 for mortality in comparison with normal diastolic function (Figure 1-16).²⁰ Abnormal LV Doppler filling parameters were also associated with high risk of incident HF over 5 year follow-up in older patients in the

Cardiovascular Health Study.⁹⁸ Thus echo parameters (or patterns) of diastolic function have strong prognostic significance, but exactly how they relate to clinical HF remains unclear.

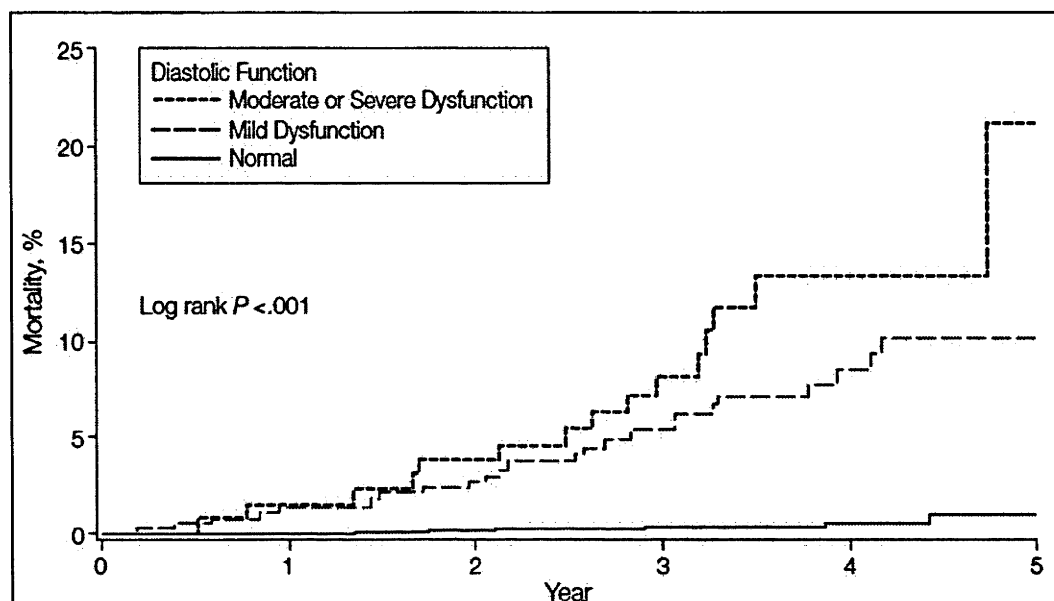


Figure 1-15 Kaplan-Meier mortality curves for subjects with normal versus abnormal diastolic function as assessed by Doppler echocardiography.

From Redfield et al.²⁰

Apart from generic advice regarding the control of risk factors, there is no evidence to advocate any specific therapy for patients with asymptomatic DD.

1.8.3 Stages of heart failure in the era of cardiac imaging

The insights into the natural history of HF that have been afforded by findings from echocardiographic surveys were acknowledged by ACC/AHA and incorporated in their guidelines for the evaluation and management of HF in 2001.¹⁰⁶ The writing committee developed a new approach to the classification of HF that emphasizes its

evolution and progression and defined four stages of HF. Patients with stage A HF are at high risk for the development of HF but have no apparent structural abnormality of the heart. Patients with stage B HF have a structural abnormality of the heart but are asymptomatic of HF. Patients with stage C HF have a structural heart disease and current or previous symptoms of HF. Patients with stage D HF have end-stage HF with symptoms that are refractory to standard medical therapy. This staged classification highlights the fact that established risk factors and structural abnormalities are necessary for the development of HF, recognises its progressive nature, and superimposes treatment strategies on the fundamentals of preventive efforts.¹⁰⁷

1.8.4 Screening for preclinical left ventricular dysfunction

To be appropriate for screening, a disease should be serious, and the preclinical phase of the disease should have a high prevalence among the population targeted for screening. Furthermore, screening initiated before a critical point in the natural history of the disease should result in treatment being initiated before the onset of symptoms (Fig. 1). This treatment should be more beneficial in reducing morbidity or mortality than treatment given after symptoms develop. Finally, the screening for the disease should not result in a significant incidence of “pseudodisease”. On the basis of these characteristics, it would appear that LV dysfunction is an appropriate disease for screening, although further studies are warranted to evaluate the benefits of treatment of preclinical LV systolic dysfunction and to determine the natural history of DD.

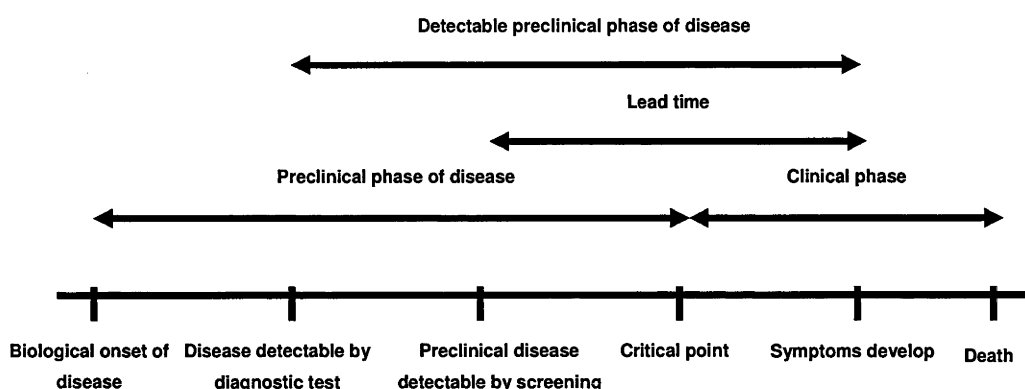


Figure 1-16 Natural history of disease: implications for screening.

The diagram can be used to evaluate appropriateness criteria for a screening test and illustrates how lead-time bias can result in apparent increase in survival attributable to screening. Adapted from Herman et al.¹⁰⁸

1.9 CONCLUSIONS

Recent advances in knowledge of the pathophysiology of LV dysfunction and its relationship between clinical symptoms of cardiac insufficiency have direct implications for the diagnosis and treatment of HF. Our challenge now is to recognise the burden of LV dysfunction in the community and identify non-invasive diagnostic strategies which would be useful for the early diagnosis of LV structural and functional abnormalities even prior to the development of overt symptoms of HF. Such aims will be addressed in the research studies which follow (chapters 4-7). To put these concepts into perspective, however, it is first necessary to review the current echocardiographic techniques available for the assessment of LV function, with particular reference to their limitations.

Chapter 2: METHODS FOR DETECTION OF LEFT VENTRICULAR DYSFUNCTION

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2.1 ABSTRACT

Patients with HF and “normal” LV ejection fraction are considered to have possible or probable HF related to LV diastolic dysfunction. A more specific diagnosis can be made by demonstrating abnormal LV diastolic function. While the various patterns of transmitral flow have been shown to have important prognostic implications, such assessments are complex and intrinsically dependent on LV loading conditions. More recent advances in echocardiographic techniques have improved our understanding of LV diastolic function and have provided a means of non-invasively estimating LV filling pressure. Because of the restricted access to echocardiography, it has been proposed that non-imaging methods for the detection of LV function be used as a filter prior to assessment. These methods may have the potential to extend their diagnostic application from diagnosis to screening high-risk populations, although further studies are required. In this chapter, I review methods for assessment of LV function. In particular, I outline the recent advances in the methods for assessment of LV diastolic function. Evidence to support the use of non-imaging methods for the detection of LV function (circulating biomarkers and measurement of arterial stiffness) is presented.

2.2 REFERENCE STANDARD FOR ASSESSMENT OF LV FUNCTION

Echocardiography is the most practical technique for determining cardiac structure and function. Further, it offers a comprehensive assessment for HF patients by allowing the evaluation of EF, haemodynamically significant valvular heart disease and pericardial disease. Doppler echocardiography is widely available, non-invasive and less expensive than other techniques, which renders it ideally suited for assessment of LV diastolic function. However, a significant limitation is the requirement for an evaluation of a complex array of haemodynamic parameters that vary with loading conditions and often provide conflicting information. This chapter will attempt to clarify this complex area, detailing the application of 2-dimensional and Doppler echocardiography for the clinical assessment of LV function. The limitations of the currently available techniques will be outlined and non-invasive approaches for the detection of subjects with LV dysfunction will be discussed.

2.2.1 LV ejection fraction as a marker of cardiac function

Ejection fraction (the percentage of stroke volume divided by end-diastolic volume) was initially adopted as an index of LV systolic function before the introduction of echocardiography and other non-invasive imaging techniques, when cardiac catheterisation was used to assess ventricular function by contrast cineventriculography.¹⁰⁹ To avoid the added effort of calibrating ventriculographic volumes, EF was born as a quick and relatively reproducible way of quantifying function.^{110, 111} Indeed, even after the advent of echocardiography, EF was used for years as the sole quantitative measure of global cardiac function.

The assessment of LV systolic function by EF is used for the diagnosis of HF in patients with symptoms of cardiac insufficiency, for the prediction of morbidity and mortality,¹¹² and as a diagnostic criterion to enable or preclude patients from receiving a variety of potentially beneficial medical therapy and procedures including cardioverter-defibrillator implantation¹¹³ and valve replacement.¹¹⁴

Despite its widespread use in the clinical setting, a number of limitations with EF as a marker of global systolic function have been recognised, relating principally to reproducibility of measurements and the sensitivity of this marker to alterations in LV systolic function. Although three-dimensional echocardiography and magnetic resonance imaging produce more reproducible measurements of EF than two-dimensional echocardiography or ventriculography,^{115, 116} no measure of EF sufficiently accounts for regional abnormalities unless several myocardial segments are involved. Recent studies have shown that longitudinal systolic function assessed using measures derived from tissue Doppler imaging is reduced in patients with HF-NEF.^{117, 118} Novel quantitative assessments of tissue velocity, strain and strain rate are now feasible on commercially available echocardiographic machines for the assessment of regional and global LV systolic function (in longitudinal, circumferentially and radial planes). However, these measures are sometimes cumbersome and time-consuming to measure and in most laboratories have less than desirable reproducibility.¹¹⁹

2.2.2 Assessment of diastolic function with echocardiography

At the time that the Canberra Heart Study was conducted, there was no consensus regarding diagnostic echocardiographic criteria for the assessment of diastolic

function, although several recommendations had been proposed.^{120, 121} The European Study Group on Diastolic HF has provided comprehensive criteria which relate to abnormal LV relaxation, abnormal LV filling or reduced LV diastolic distensibility based on transmitral and pulmonary vein Doppler data.¹²⁰

2.2.2.1.1 Limitations with conventional Doppler examination

Echocardiographic evaluation of diastolic function has been traditionally performed by measurement of transmitral flow parameters including the early (E) and late (A) diastolic filling velocities, the E/A ratio and the E deceleration time from an apical 4 chamber view with conventional pulsed wave Doppler (Figure 2-1a).¹²¹ The transmitral E wave is related to the time course of active LV relaxation which generates a pressure gradient from the left atrium through the LV inflow tract to the LV apex.¹²² Early diastolic LV filling is therefore largely influenced by interaction of left atrial (LA) compliance and the rate of ventricular relaxation. The peak E velocity may be increased by either elevated LA pressure (the cause of high E/A ratios in cardiac disease), or alternatively, by low LV minimal diastolic pressure due to rapid LV relaxation (which drives the high E/A ratios typical of normal young adults).¹²³

Based upon the interpretation of the transmitral flow profile, diastolic function is initially classified as either normal, impaired relaxation, pseudonormal, restrictive (which may be reversible or non-reversible with preload reduction), or indeterminate (if normal or pseudonormal cannot be differentiated) (Figure 2-1). These patterns of LV filling represent progressively worse DD as the LV becomes increasingly abnormal. It is important to consider that increasing DD is usually accompanied by a progressive increase in LV filling pressures, which in turn have a major impact on

the transmitral flow profile. Slow or prolonged LV relaxation therefore causes a decrease in E velocity but at the same time contributes to elevation of LA pressure which in turn tends to increase the E velocity.¹²⁴ These opposing effects of LA pressure and LV relaxation are also operative on the E deceleration time, which tends to be prolonged by impaired LV relaxation and shortened by increased filling pressures. Thus the effects of DD on the E/A ratio and E wave deceleration time become progressively compensated and then over-compensated by the effects of loading, resulting in a non-linear (in fact “U” shaped) relationship between these indices and severity of DD.¹²⁵ The isovolumic relaxation time bears a similar relationship to DD and load and does not provide additional information. In individual patients therefore, the filling pattern can change from mild (impaired relaxation) to more severe (pseudonormal or restrictive) DD with either a progression of the underlying pathophysiological process, or alteration of loading conditions (Figure 2-2). Similarly, improvement in the Doppler filling profile may occur over a longer period with treatments targeting the underlying cause. Thus transmitral flow parameters must be further interpreted in the light of LV loading. This requires either incorporation of alternative load-dependent parameters, or use of newer less load-dependent techniques (or preferably both).

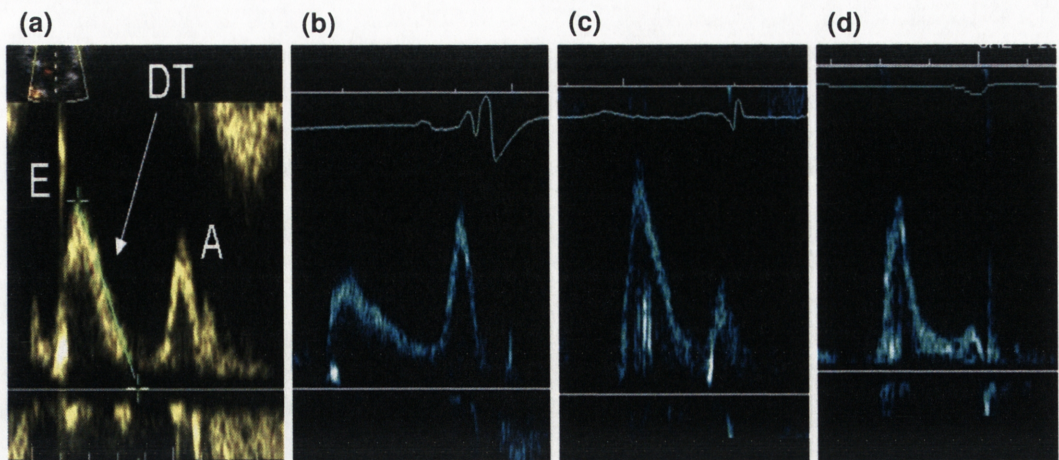


Figure 2-1 Pathophysiological characterisation of left ventricular filling patterns.

(a) Normal transmitral flow in a patient in sinus rhythm. (b) Impaired relaxation with normal filling pressures. (c) Pseudonormal filling. (d) Restrictive filling.

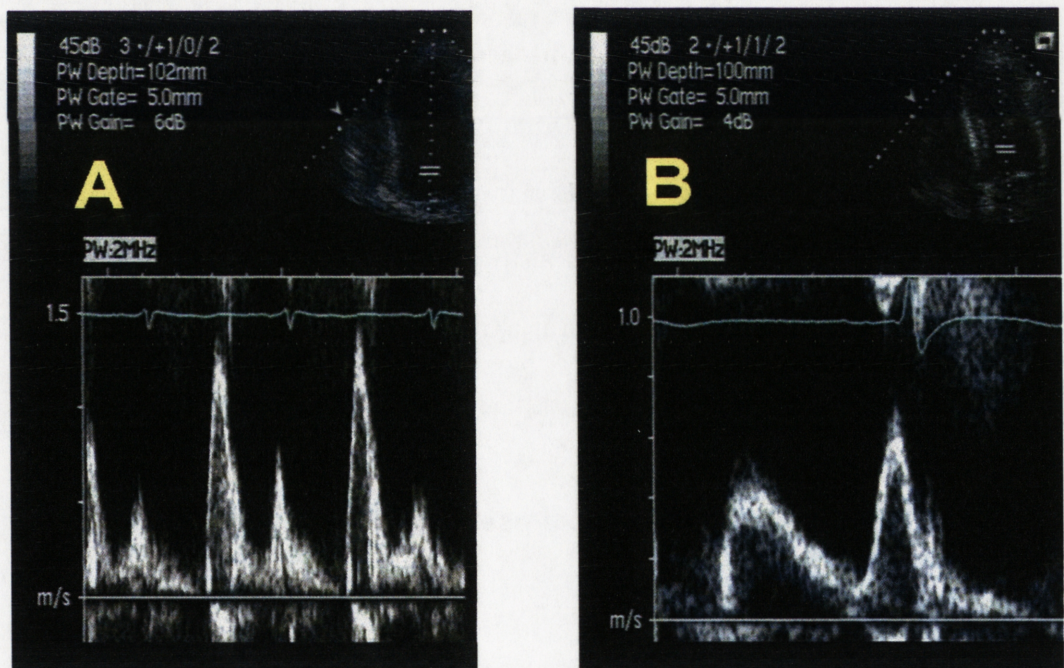


Figure 2-2 Load-dependence of the left ventricular filling pattern.

A. Restrictive filling associated with increased preload in a HF patient with fluid overload. B. Following diuretic therapy, removal of intravascular volume has reduced LV filling pressure and unmasked the underlying impaired relaxation pattern.

2.2.2.1.2 Impaired left ventricular relaxation

Slowing and prolongation of LV relaxation becomes apparent at an early stage of LV dysfunction,¹²⁶ perhaps because this part of the cardiac cycle is metabolically very demanding. Impaired LV relaxation reduces the peak transmitral pressure gradient, thereby reducing the E velocity and E/A ratio.¹²⁰ Continued slow or discoordinate LV relaxation maintains a low transmitral pressure gradient into mid diastole resulting in prolongation of the E deceleration slope¹²⁰ (Figure 2-1b). As LA pressure remains relatively normal at rest in this early stage of DD, patients may have symptoms only with exertion, and transmitral flow may be close to normal at rest. Importantly, even this mild degree of DD places patients at increased risk for adverse cardiovascular events.^{20, 127} However, the functional significance of an impaired relaxation pattern of LV filling is less clear, and estimation of resting LV filling pressures in this group is independently predictive of exercise capacity.¹²⁸

2.2.2.1.3 Differentiating normal from pseudonormal LV filling

Pulmonary venous pulsed wave Doppler, tissue Doppler imaging of the mitral annulus, and the response of E/A to Valsalva manoeuvre can be used to distinguish normal from pseudonormal LV filling patterns.¹²³

Pulmonary venous flow

The pulmonary venous Doppler signal comprises “forward” systolic (S) and diastolic (D) velocities into the left atrium, and a “backwards” late-diastolic A reversal wave corresponding to atrial contraction. The major factors influencing the pulmonary venous Doppler profile are illustrated in Figure 2-3. In older adults, systolic flow is dominant such that S/D is >1 .¹²⁹ Like the E and A velocities in the transmitral Doppler profile, the pulmonary venous S/D ratio exhibits a non-linear relationship to progressive DD. flow pattern.

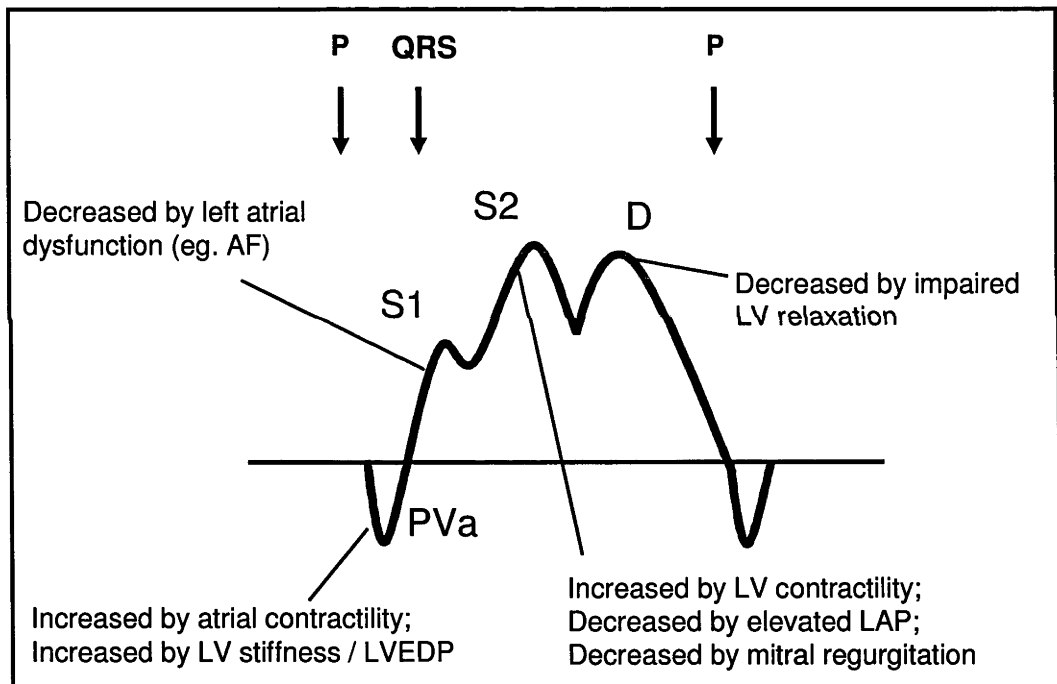


Figure 2-3 Determinants of the pulmonary venous Doppler profile.

AF = atrial fibrillation, LAP = left atrial pressure, LVEDP = left ventricular end-diastolic pressure, PvA = pulmonary venous A reversal.

The pulmonary venous A wave provides an additional tool for assessment of LV filling pressure and diastolic function. The peak A reversal velocity increases as resistance to atrial forward flow increases as a result of increased ventricular stiffness and/or end-diastolic pressure, such that a peak velocity >35 cm/s is suggestive of elevated filling pressures.¹²¹ However, LA mechanical dysfunction often accompanies advanced DD (particularly in association with paroxysmal atrial fibrillation) and may lead to low A reversal velocities. A more robust pulmonary venous parameter may be derived from the difference in the transmitral and pulmonary venous A wave durations. As LV compliance decreases and diastolic pressure rises, increased afterload on the left atrium tends to shorten the transmitral A wave, while its duration measured in the pulmonary vein may be increased. A difference in the respective durations of >20-30 msec accurately predicts significant elevation of LV end-diastolic pressure¹³⁰ and may be an early marker of transformation from impaired relaxation to a pseudonormal filling pattern. The major advantage of this parameter is its utility in the setting of preserved LV systolic function,^{131, 132} while the obvious limitation is the difficulty in acquisition of accurate measurements of the pulmonary venous A duration from a transthoracic window.¹³³

Load-altering manoeuvres

The principle behind this step is to remove the effects of preload compensation and thereby unmask the underlying relaxation abnormality. Thus the aim is to produce a transient lowering of left heart filling pressures which in the clinical setting is most practically achieved with the Valsalva manoeuvre, although a similar effect may be obtained with sublingual nitroglycerin.¹³⁴ During the Valsalva manoeuvre, an initial

minor increase in systemic BP (due to increased pulmonary venous return) is followed by a decrease in systemic venous return and a gradual decrease in stroke volume, leading, after a few cardiac cycles, to a reduction in LA and LV filling pressures and potential “conversion” of pseudonormal filling to an impaired relaxation pattern.¹³⁵ This approach remains largely qualitative, and the required decrease in either the E velocity or the E/A ratio to reach a diagnostic threshold varies with different studies and will depend upon the baseline values for E and A, the quality of Valsalva, degree of patient effort and other factors.¹³³ Even in the research setting, ability to obtain adequate data may be particularly low,^{133, 136} thus limiting the sensitivity of the technique. A reduction of E velocity by 50% or complete reversal of the E/A ratio to <1 may be useful criteria,¹³⁷ although other investigators have been unable to determine an accurate cutoff.¹³⁶

Tissue Doppler imaging - long axis relaxation rate

Long-axis shortening (contraction) and lengthening (relaxation) of myocardial segments results in longitudinal motion of the mitral annulus toward or away from the (relatively fixed) LV apex during systole and diastole respectively. Although long-axis segmental shortening remains fairly uniform along the myocardial wall,¹³⁸ a gradient of increasing velocity from apex to base has been demonstrated.^{139, 140} Mitral annular velocities may therefore be regarded as an “aggregate” of segmental myocardial velocities and in the absence of regional LV dysfunction accurately reflect global long-axis LV function. The systolic velocity (Sa) corresponds to ventricular ejection whilst Ea and the late diastolic velocity (Aa) correspond to the transmitral Doppler flow. In normal subjects the Ea occurs coincident with, or just

before, the transmitral E wave, whereas in HF there is a progressive delay in Ea with respect to E.¹²² Of more practical importance, the Ea velocity progressively decreases as the long-axis relaxation rate becomes increasingly slower in the setting of a wide range of cardiac disease processes including dilated, restrictive and hypertrophic cardiomyopathies. Invasive studies have demonstrated that the Ea velocity correlates strongly with the time constant of isovolumic relaxation over a wide range of filling pressures.¹⁴¹⁻¹⁴³ Specifically, the Ea velocity is much less susceptible to the effects of increased preload and remains low in patients with advanced DD and pseudonormalisation of the transmitral E velocity.^{143, 144} Further, Ea is typically lowest in patients with severe LV dysfunction and restrictive filling.

The most commonly used technique is to use pulsed wave TDI to record longitudinal velocities at the mitral annulus, whereby a sample volume (2-5 mm) is placed at the septal or lateral border of the mitral annulus in an apical 4 chamber view.¹²⁵ If obtaining only a single measurement, the lateral Ea may be preferred as the septal Ea velocity has been demonstrated to be altered by preload in subjects with normal LV function,¹⁴⁵ although this effect may decrease as LV relaxation becomes progressively impaired.¹⁴⁶ In addition, the septal Ea velocity may be influenced by right ventricular diastolic function. Potential pitfalls to be considered when acquiring and interpreting pulsed wave TDI signals include ensuring that the 2-D image quality is optimised and that the ultrasound beam is well aligned (<30 degrees) with the direction of longitudinal motion (which may be more challenging at the lateral annulus). Finally, localised segmental hypokinesis in a given LV wall will result in

reduced velocity of annular motion at the corresponding site, possibly leading to a spuriously low estimate of global LV function.

Tissue Doppler imaging - estimation of LV filling pressures

As discussed, progressive DD is associated with both impairment of LV relaxation and an increase in LA pressure. These concurrent events tend to have opposing effects on the transmitral E velocity, rendering it poorly predictive of either process. However, the E velocity (which increases with elevation of LA pressure) may be “corrected” for the degree of impairment in LV relaxation rate by relating it to the Ea velocity (which is a relatively load-independent measure of reduced LV relaxation) to provide an index, the E/Ea ratio, which has been demonstrated to correlate with mean LA pressure.¹⁴¹ This concept has been validated in various clinical conditions including normal and impaired systolic function, tachycardia, atrial fibrillation, and hypertrophic cardiomyopathy.^{133, 141, 147-149} This application of TDI for estimation of LV filling pressures has significantly advanced the ability of the echocardiographer to distinguish normal from pseudonormal LV filling.

As discussed for assessment of LV relaxation rate, the lateral Ea may be preferable for E/Ea ratio estimation of filling pressure as more defined cutoffs have been reported. Nagueh et al demonstrated that $E/Ea > 10$ using the lateral mitral annular velocity reliably predicts a pulmonary capillary wedge pressure of $>12\text{mmHg}$.¹⁴¹ In comparison, using the septal Ea velocity, Ommen et al found that while pulmonary capillary wedge pressure is likely normal if the E/Ea ratio is <8 and likely elevated if >15 , intermediate values were less useful.¹³³ A recent report found lateral E/Ea to be superior to septal E/Ea for predicting wedge pressure when EF is $>50\%$,¹⁵⁰ although

an average of both values is more accurate in the presence of regional dysfunction.^{150, 151}

2.2.2.1.4 Restrictive filling

Restrictive filling, characterised by a marked increase in the E/A ratio and shortening of the E deceleration time, indicates severely reduced LV compliance and marked elevation of LA pressure. In the setting of preserved EF, restrictive filling usually indicates severe infiltrative myocardial disease such as cardiac amyloidosis rather than hypertensive heart disease. In clinical practice, restrictive filling is most commonly seen in association with LV dilatation and severe systolic dysfunction and is strongly predictive of mortality in this population, particularly if it is not reversible with treatment.¹⁵²

2.2.3 Left atrial volume as an expression of LV filling pressures

In subjects without primary atrial pathology or congenital heart or mitral valve disease, increased LA volume usually reflects elevated ventricular filling pressures. During ventricular diastole, the LA is exposed to the pressures of the LV. With increased stiffness or noncompliance of the LV, LA pressure rises to maintain adequate LV filling,¹⁵³ and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium. Thus, LA volume increases with severity of DD.^{154, 155} The structural changes of the LA may express the chronicity of exposure to abnormal filling pressures^{155, 156} and provide predictive information beyond that of diastolic function grade,¹⁵⁷ which is determined from evaluating multiple load-dependent parameters and therefore reflective of the instantaneous LV diastolic function and filling pressures. In this way, analogous to the relationship

between hemoglobin A1C and random glucose levels, LA volume reflects an average effect of LV filling pressures over time, rather than an instantaneous measurement at the time of study.¹⁵⁸ Thus, Doppler and tissue Doppler assessment of instantaneous filling pressure is better suited for monitoring haemodynamic status in the short term, whereas LA volume is useful for monitoring long-term haemodynamic control.

2.3 ALTERNATIVE IMAGING TECHNIQUES

Whilst echocardiography remains the tool of choice in the clinical arena, and is the only acceptable method for the comprehensive assessment of cardiac structure and function in surveys of the general population, other imaging modalities may be required in subjects with limited echocardiographic windows or poor quality echocardiographic data.

Cardiac catheterization

Invasive measurement of cardiac function by cardiac catheterization is often invoked as the gold standard method for assessment of cardiac function.⁶³ However, this method is not utilized as the main method for assessment of cardiac function in the clinical arena because of the cost, complexity, and expertise required, as well as patient risk and lack of tolerability associated with this invasive procedure. Unlike echocardiography, cardiac catheterization does not lend itself to serial assessment for monitoring disease progression and response to treatment.

Magnetic resonance imaging has recently been demonstrated to be a sensitive marker for the detection of global DD.¹⁵⁹ Although spatial resolution using this technique is

excellent, diastolic function assessment with magnetic resonance is currently limited by its inadequate temporal resolution.

Although radionuclide techniques have been used to assess properties of diastolic function, these are limited by the risk of exposure to high radiation doses, low frame rates, background lung blood pool attenuation and cycle length variability.

2.4 THE NEED FOR A NON-IMAGING TEST FOR ASSESSMENT OF LV FUNCTION

Given the complexity of the echocardiographic evaluation of LV function and the restricted access to echocardiography, it has been proposed that non-imaging methods for the detection of LV function be used as a filter prior to assessment. These methods may have the potential to extend their diagnostic application from diagnosis to screening high-risk populations, although further studies are required.

2.4.1 Circulating biomarkers of LV function: Natriuretic Peptides

The clinical utility of the circulating biomarkers in HF can be judged according to the satisfaction of three key criteria. Firstly, the proposed biomarker must be accessible, reliable, and affordable. Secondly, the marker must provide incremental information about cardiac function and prognosis that would not otherwise be available. Finally, patient management with the biomarker should result in improved clinical outcomes. Despite many promising candidates, only the natriuretic peptides currently have the potential to satisfy these requirements.

B-type natriuretic peptide (BNP) is a 32-amino acid peptide, which is derived from cleavage of a prohormone (pro-BNP) and is secreted primarily from the ventricular myocardium in response to dilatation and increased intra-cavity pressure.^{160, 161} Whilst the primary role of BNP appears to be body fluid homeostasis and BP control through its diuretic, natriuretic, and vasodilator effects, evidence suggests that BNP can also modulate cellular proliferation and may act as a local regulator of ventricular fibrosis and remodelling.¹⁶²⁻¹⁶⁵

Elevation of BNP has been demonstrated in the setting of acute HF, and correlates with the degree of reduced EF.^{166, 167} Promising results from a number of relatively small single-centre studies^{166, 168} led to a large multi-center study evaluating the utility of a commercially available BNP test in the evaluation of acutely dyspnoeic patients in the emergency department. Of the 1586 study patients, 744 (47%) were ultimately assigned to have HF by a panel of two cardiologists who reviewed results of the diagnostic evaluation. A BNP of 100 pg/ml was shown to be highly accurate for the diagnosis of acute HF-rEF.¹⁶⁷ The diagnostic accuracy of a clinical judgment was 74%, while that of BNP was 81%.¹⁶⁹ Based on Bayesian analysis, it appears that BNP was most useful when the clinical diagnostic accuracy of HF is intermediate.

BNP and NT-proBNP perform similarly for the diagnosis of HF in acutely dyspnoeic patients.¹⁷⁰ NT-proBNP may have benefits due to the “high-throughput” assay platform, the convenience of testing NT-proBNP levels on stored serum as a post-hoc assessment, the lower assay variability, and lower costs.¹⁷¹

In a landmark study, McDonagh et al provided the first report on the use of natriuretic peptide levels to screen for ventricular dysfunction in the population.¹⁷²

BNP levels were higher in persons with systolic dysfunction as compared to those without systolic dysfunction regardless of clinical HF status. The area under the receiver operating characteristic curve for detection of systolic dysfunction by BNP was 0.88. However, as the prevalence of systolic dysfunction was low at 3% (and thus, the probability of not having systolic dysfunction was 97%), the probability of not having systolic dysfunction with a normal BNP was 97.5%. Thus, the *incremental* value of a normal BNP as a test to further “rule out” systolic dysfunction was low. A post-hoc analysis of these data divided the population according to risk using clinical parameters and defines a “low-risk” (prevalence of systolic dysfunction 0.7%), “moderate-risk” (prevalence of systolic dysfunction 6.0%), and “high-risk” group (prevalence of systolic dysfunction 19%).¹⁷³ A low BNP concentration with high sensitivity was used as a partition value to rule out systolic dysfunction. With this strategy, use of BNP coupled with echocardiography when BNP is abnormal was more cost-effective than echocardiography alone to screen for systolic dysfunction even though echocardiography was needed in 60-70% of the higher risk groups due to the low specificity of the most sensitive BNP value. In this analysis, BNP serves to “rule out” systolic dysfunction in a minority of the screened population, eliminating the need for echo in that segment. Others have advocated a “rule-in” strategy where a screening test should identify a small segment of the population at much higher risk of having the disease screened for, thus focusing use of definitive diagnostic testing on that much smaller segment of the population.^{174,}

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The most comprehensive assessment of the potential value of BNP as a screening test for pre-clinical systolic dysfunction or LV remodelling comes from the Framingham

Heart Study.¹⁷⁴ Investigators concluded that BNP did not appear promising as a screening tool for systolic dysfunction or elevated LV mass in the general population or in higher risk subsets of the general population.

While a number of studies had reported on the use of BNP for diagnosis of HF, there were relatively few data regarding normal values in persons free from cardiovascular disease or ventricular dysfunction. Furthermore, at the time the Canberra Heart Study was commenced, there was no population-based data to assess the value of natriuretic peptides for the diagnosis of DD. Lubien et al studied the correlation of BNP levels with Doppler evidence of DD in subjects referred for echocardiography for evaluation of ventricular function and indicated that using BNP may help identify DD.¹⁷⁶ However, the potential for selection bias to adversely affect the validity of that clinic-based study was high.

2.4.2 Pulse wave assessment of central (aortic) arterial stiffness

As discussed in chapter 1, hypertensive heart disease is associated with abnormal vascular function, and increased arterial stiffness has been implicated in the pathogenesis of HF-NEF. Although further research is needed, newer approaches to HF may therefore benefit from evaluation of arterial properties. Arterial stiffness can be assessed noninvasively using the following methods: 1) relating change in vessel size (diameter or area) to distending pressure, 2) estimation of pulse wave velocity, 3) pulse waveform analysis.

The relation of change in vessel size to distending pressure provides a measure of local arterial stiffness, and is most commonly measured on superficial arteries using echo-tracking techniques. Local PP should be measured at the site of the distension measurement, such as carotid artery. The use of brachial BP in calculation of these indices may introduce systematic errors, particularly in younger subjects in whom brachial PP is significantly greater than carotid PP. Applanation tonometry can be used to estimate carotid BP in these circumstances.¹⁷⁷ Magnetic resonance imaging (MRI) techniques have also been used to measure vascular distensibility and compliance.¹⁷⁸ A distinct advantage of MRI is that it can be used to measure diameter and distension of deeper arteries such as the aorta. However, it lacks temporal resolution, remains expensive and the limitations relating to accurate and simultaneous quantitation of local arterial pressure are equally applicable to MRI.

Perhaps the simplest measure of arterial stiffness is pulse-wave velocity, the speed of propagation of the pressure wave along the large arteries following ventricular ejection. PWV has emerged as the “gold-standard” measurement of regional arterial stiffness.¹⁷⁹ The theoretical basis of PWV as a measure of arterial stiffness is described by the Moens-Korteweg equation: $PWV^2 = E \cdot h / 2r\rho$; where E is the slope of the stress-strain relationship for a given vessel, Young’s modulus; ρ is the density of fluid; and $h/2r$ is the wall thickness/diameter. In practice, PWV is calculated by measuring the time taken for the arterial waveform to pass between two points a measured distance apart, and involves taking readings from the two sites simultaneously or gating separate recordings to a fixed point in the cardiac cycle, usually the R wave of the electrocardiogram. Arterial pulse waves can be detected by

using Doppler ultrasound (the pressure pulse and the flow pulse propagate at the same velocity), or applanation tonometry. Central PWV of large elastic arteries, such as the aorta, increases with age non-linearly, being more prominent in subjects of age greater than 50 years (Figure 1),¹⁸⁰ whereas peripheral PWV in the muscular arteries of the limbs does not increase with age.¹⁸¹ Accurate PWV quantitation is dependent on accurate measurement of the distance between recording sites. Increasing tortuosity of the abdominal aorta with age may lead to a systematic underestimation of PWV. Because PWV is also determined by distending BP, it is important to adjust for the effects of mean BP before estimating the independent influence of arterial stiffness on outcomes of interest.

Pulse wave analysis (PWA) is performed using applanation tonometry or echo tracking. From PWA, indexes of wave reflection such as augmentation pressure (AP; the difference between the first and second systolic peaks) and augmentation index (AIx; the quotient of AP on PP expressed as a percentage) can be derived. In healthy young persons, central systolic BP is significantly lower than peripheral systolic BP, whereas diastolic BP remains steady throughout the arterial tree.¹⁸² This phenomenon is called PP amplification. However, in older persons, PP amplification is diminished as a consequence of arterial stiffening.¹⁸³ Thus, central BP is often not represented by brachial BP. Since it is central BP that directly affects target organ function, there is expert consensus¹⁷⁹ that PWA should be optimally obtained at the central level using the application of a generalized arterial transfer function to the radial artery waveform to reconstruct the corresponding central pressure waveform and derive an approximation of central BP.¹⁸⁴ Despite continued controversy regarding the validity

of this approach,^{185, 186} the estimation of central pressures has been increasingly used as a risk marker and surrogate outcome in epidemiological^{187, 188} and intervention^{189, 190} studies. A review of clinical studies indicating the independent value of central haemodynamics in these roles and as a predictor of adverse CV events has recently been published.¹⁹¹

It should be acknowledged that AIx is not a simple surrogate measure of large artery stiffness as it is influenced by several other factors that modulate ventricular-vascular coupling. AIx is inversely related to acute changes in heart rate,¹⁹² which result in a decrease in ejection duration, and a reflected wave that arrives later in the cardiac cycle. To account for differences in heart rate, AIx can be reported as an index that is normalized for a heart rate of 75 beats per minute (AIx@75). AIx is inversely influenced by body height, EF, peripheral vascular resistance and increases non-linearly with age¹⁸⁰. Contrary to PWV, however, the positive relation between age and AIx is more prominent in subjects of age less than 50 years, with minimal rise in AIx observed after the age of 65 years (Figure 1).^{180, 181} Not surprisingly, a dissociation between AIx and PWV has been described,¹⁹³ and the two measures should be considered to be complementary rather than interchangeable.¹⁷⁹ Further studies will be required to define the optimal approach to combine these measures in order to characterise arterial function in an individual.

2.4.2.1.1 Determinants and consequences of arterial stiffness

Traditional CV risk factors such as ageing,^{177, 194} HT,¹⁷⁷ diabetes mellitus,¹⁹⁵ dyslipidemia,¹⁹⁶ smoking¹⁹⁷ and sedentary lifestyle¹⁹⁸ promote an increase in arterial stiffness. With ageing and elevated BP, the arteries stiffen as the result of

degeneration of the arterial media with fractures and fragmentation of elastic lamellae, increased collagen and calcium content, and dilation and hypertrophy of large arteries and the aorta.¹⁹⁹ Such alterations are more pronounced in central (thoracic aorta, carotid) than in peripheral (femoral, radial) arteries.¹⁷⁷ In addition to structural alterations caused by repeated cycles of arterial distension and recoil, the accumulation of advanced glycation end products in the arterial wall plays an important role in the development of arterial stiffness with ageing. AGE can also promote the development of arterial stiffness through impairment of endothelial function²⁰⁰ and promotion of inflammation.²⁰¹

With an increase in arterial stiffness, there is less cushioning of stroke volume in the arterial bed during systole. Consequently, a greater proportion of stroke volume is forwarded to the periphery such that the amplitude of the arterial pulse wave during systole rises and diastolic pressure falls (Figure 2). Exposure to higher pulsatile stress is particularly deleterious in organs with low impedance beds, such as the brain and the kidney, resulting in accelerated microvascular disease²⁰² and consequent deterioration of cognitive²⁰³ and renal²⁰⁴ function.

2.4.2.1.2 Arterial stiffness for the prediction of cardiovascular outcomes

Brachial PP, an index of global arterial stiffness, is an established marker of CV risk.²⁰⁵ More recently, there has been an accumulation of data confirming the relationship between indices of regional arterial stiffness and the development of adverse CV outcomes in community-based subjects and high-risk patients with overt CV disease.

General Population. The prognostic value of PWV in the general population has been documented in recent studies. Increased PWV was independently predictive of CV events, including CAD, stroke and CV death in 1678 population-based subjects.²⁰⁶ For each 1-SD increment in PWV, the risk of an event increased by 16 to 20%. In a separate study of 2835 healthy subjects, PWV was an independent predictor of both stroke and CAD after adjustment of various factors including carotid intima-media thickness, MBP and PP.²⁰⁷ Interestingly, in these studies, brachial PP (by single office measurement and 24-hour ambulatory monitoring) was not associated with a CV event after adjustment of PWV. It is possible that the superiority of PWV to brachial PP for risk stratification in the general population may be related to PP amplification, which differentially affects younger subjects and will diminish the utility of PP as a marker of CV risk in an adult population with wide age ranges.¹⁸³

Hypertension. The predictive value of arterial stiffness has been evaluated in preclinical subjects with classical CV risk factors such as HT. PWV was associated with incident CV disease including coronary events (odds ratio [OR] = 1.34 per 3.5m/s increment in PWV)²⁰⁸ and stroke (OR=1.39 per 4.0m/s increment in PWV)²⁰⁹ in hypertensive patients without overt CV disease. Furthermore, it was determined that PWV, but not brachial PP, was predictive of CV mortality, independent of age, prior CV disease and diabetes (OR=1.51 per 5m/s increment in PWV).²¹⁰ There is scant evidence to support the incremental value of assessment of arterial stiffness to guide therapy in preclinical subjects with HT. Treatment-induced changes in surrogate outcomes such as indexed left ventricular (LV) wall mass²¹¹ and carotid

intima-media thickness²¹² were correlated with changes in AIx, independently of brachial BP measurement. Further studies are required to examine whether markers of arterial stiffness can be utilized in strategies to identify “high-risk” patients, who may be more likely to benefit from intensive medical therapy in order to prevent the development of subsequent adverse clinical outcomes.

Elderly. An age-related increase in arterial stiffness attenuates the difference between central and peripheral PP. Accordingly, brachial PP represents a robust and easily measured marker of CV risk in elderly subjects. In contrast, because there is minimal increase in AIx after the age of 65 years,^{180 181} the value of this index of arterial stiffness as a marker of CV risk is diminished in older persons.²¹³ PWV remains an important prognostic marker in the elderly. In a large cohort of 2488 elderly persons, PWV was predictive of CV death, CAD and stroke after adjustment of age, BP, creatinine, prior CV disease and CV risk factors.²¹⁴

Coronary artery disease. In patients undergoing coronary angiography, increased arterial stiffness is related to prevalent CAD.²¹⁵ Moreover, assessment of arterial wave reflections and central BP may be more useful for prediction of CAD extent and severity than peripheral pressures and PWV, however, this observation varies according to the age of the study population. For instance, Weber et al demonstrated that a significant relationship between AIx and the risk of CAD was observed only in younger patients of age <60 years. In patients with established CAD, AIx was associated with the development of major adverse CV events after percutaneous coronary intervention, independent of clinical risk factors including lesion complexity, brachial systolic BP and PP (relative risk of 1.8 per AIx@75 tertile).

Renal Disease. The majority of deaths in patients with kidney disease are attributed to CV events.²¹⁶ In end-stage renal disease (ESRD), several abnormalities in the microcirculation have been reported, including rarefaction of vessels, increased ratios of wall to lumen of small arterioles, and decreased endothelium-mediated vasodilation.²¹⁷ Consequently, patients with ESRD have much stiffer arteries compared to controls of the same age and BP.²¹⁸ The relationship between arterial stiffness and CV death has been evaluated in patients with ESRD using a variety of methods, including arterial distensibility, PWV and PWA.^{219 220} Aortic PWV is significantly correlated with CV death independently of BP (OR=5.9 for those with PWV >12m/s compared to the referent group with PWV <9.4m/s).²¹⁹ Moreover, a reduction in PWV of 1 m/s with BP control was associated with a 21% reduction in the risk of CV death.²²⁰ In contrast, baseline and change in systemic BP referent group with PWV <9.4m/s).²¹⁹ Moreover, a reduction in PWV of 1 m/s with BP control was associated with a 21% reduction in the risk of CV death.²²⁰ In contrast, baseline and change in systemic BP were not predictive of CV death. PWA has also been reported as a useful index for the prediction of CV outcomes in ESRD patients.²²¹ There is limited information regarding the prognostic value of arterial stiffness in patients with mild to moderate renal disease.

Heart Failure. The relationship between arterial stiffness and CV mortality has not been evaluated in patients with HF. However, in HF patients with preserved⁸⁵ and reduced EF²²², there is evidence that arterial stiffness is related to exercise capacity, which is an important determinant of mortality in these patients.²²³ There are a number of mechanisms whereby increased arterial stiffness can adversely affect

exercise capacity. First, arterial input impedance is an important determinant of left ventricular stroke work and cardiac output,²²⁴ and increased large artery stiffness reduces the ability to generate adequate cardiac output during exercise. Consequently, patients with increased arterial stiffness have lower systolic reserve in response to exercise.⁸³ Second, recent studies have documented a relationship between arterial stiffness and DD,^{225 226} which adversely affects exercise capacity through a decrease in stroke volume reserve²²⁷ and is associated with an exaggerated increase in LV filling pressure during exercise.¹²⁸ Lastly, increased arterial stiffness, through its reduction of central diastolic BP and coronary perfusion pressure, may promote subendocardial ischemia.²²⁸

2.5 CONCLUSIONS

Descriptive epidemiological data on LV dysfunction are necessary for a better understanding of the natural history of HF, and are important for guiding health policy and monitoring trends of the impact of disease over time. Echocardiography is the most feasible and acceptable method for the assessment of cardiac structure and function in surveys of the general population. The contemporary assessment of LV function by echocardiography includes a comprehensive assessment of diastolic function and filling pressures through the integration of conventional and tissue Doppler measurements. In chapter 4, I present the first Australian population-based data on the prevalence of HF and LV systolic dysfunction (EF<50%). One of the first estimates of the burden of DD in the community is presented in Chapter 5. Non-imaging methods that could accurately identify subjects with LV dysfunction may be

useful as filters prior to referral for echocardiography. In chapters 5 and 6, I evaluate the performances of NT-proBNP and PWV for the detection of LV dysfunction in the community.

Chapter 3: METHODOLOGY

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Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TSM. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;47:1018-23

3.1 DEVELOPMENT OF STUDY PROTOCOL

The study design and methodology were developed under the supervision of Professors Wayne Smith and Anne-Louise Ponsonby as part of my Doctorate of Population Health (DrPH) coursework requirements (Research Methods II). The choice of a sample frame that was population-based rather than clinic-based (albeit “open access”²²⁹) was predicated by recognition that this approach would maximize the external validity of our research, and thus increase the significance and generalisability of the results of the various studies that emanated from the research.

3.2 SOURCES OF FUNDING

The cross-sectional study was supported by a grant from the Canberra Hospital Salaried Medical Officers’ Private Practice Trust Fund. Research specific to the assessment of vascular function (chapter 7) was supported by a Cardiovascular Lipid grant awarded by the Australian Physicians Independent Committee (APIC). The author was the principal investigator in both applications for funding. In-kind support was provided by Siemens Ultrasound, who loaned the 128XP echocardiography machine for the duration of the research; and Roche Diagnostics, who provided the immunoassay kits and analysis machine for the assessment of aminoterminal B-type natriuretic peptide.

3.3 SAMPLING FRAME

The sampling frame for the study population was the electoral roll of Statistical Divisions in the Southern Districts of the Australian Capital Territory (South Canberra, Woden Valley, Weston Creek and Tuggeranong). The author applied to the Australian Electoral Commission for permission to obtain an electronic list of names and postal addresses of residents of these statistical divisions who were of age 60-85 years in January 2002. This approach was considered to be the most efficient in obtaining a sampling frame that was population-based.

3.4 RECRUITMENT STRATEGY

The recruitment strategy was based on a modification the Dillman approach.⁽²²⁾ In a previous study, it was noted that a telephone contact made soon after mail-out of the second contact letter was found to be an effective and cost-efficient way of recruitment of participants.²³⁰

At the time of the initial mail-out of invitations, the author was interviewed by the health reporter at The Canberra Times, and held live interviews on consecutive mornings with ABC Radio (AM Radio, Canberra) and 2CC (AM Radio, Canberra). This was coordinated with the assistance of Mr. Trevor Sharkie, who was the Public Relations Office at Canberra Hospital. The aim was to promote the study in the media using an approach that would be most likely to reach the demographic representative of the Canberra Heart Study population.

3.5 SAMPLE SIZE CALCULATION

Sample size calculations were based on the precision of estimates of:

- i. prevalence rates of HF and left ventricular dysfunction in the community;
- ii. diagnostic performance of aminoterminal pro-B-type natriuretic peptide for the detection of systolic and diastolic dysfunction.

Data from the Framingham cohort study provided estimates of age, sex-specific prevalence rates of HF.⁽²⁶⁾ The rates were comparable with those of a more contemporary cross-sectional study that was published just prior to our study.⁽⁸⁾ Based on these data, the expected rate of HF-rEF (termed at that time “systolic HF”) in the study population would be approximately 4%. We estimated that the prevalence of HF-NEF (termed at that time “diastolic HF”) would be approximately 2%, on the basis of extrapolation from results of the Framingham cohort study and hospital-based studies.

At the time of our research protocol development, there were no published population-based studies to estimate the performance of aminoterminal pro-B-type natriuretic peptide as a diagnostic/screening test for HF. There was one study that estimated the sensitivity and specificity of the carboxy-terminal of B-type natriuretic peptide (BNP) in a randomly selected Glasgow population aged 25-75.⁽²⁰⁾ The unusually strict definition for left ventricular systolic dysfunction was an echocardiographic assessment of LVEF<30%. The sensitivity and specificity of BNP in detecting systolic was 89% and 71%, respectively. However, based on the fact that aminoterminal pro-B-type natriuretic peptide dysfunction has a longer circulating

half life,²³¹ it had been proposed that the expected performance of aminoterminal pro-B-type natriuretic peptide in detecting HF would be superior to BNP, although this had not been confirmed in clinical studies.

In contemporary population-based prevalence studies of HF, the participation rates have been approximately 50-65%. However, with our proposed recruitment methods (modified Dillman method) and the qualities of our study population (mostly retired from work; higher education levels; older age and more likely to benefit from information derived from the study assessments), we assumed that the participation rate for our study would be at least 60% and as high as 75%.

A sample size of 1200 participants would achieve the following levels of precision (point estimates and 95% CI calculated using the exact binomial method [absolute numbers] are presented):-

- i. prevalence of “systolic HF” - 4% (3.1-5.1) [48/1200]
- ii. prevalence of “diastolic HF” - 2% (1.4-2.8) [24/1200]
- iii. overall prevalence of HF- 6% (4.9-7.3) [72/1200]
- iv. aminoterminal pro-B-type natriuretic peptide sensitivity for “systolic HF” - 90% (80-96) [43/48]
- v. aminoterminal pro-B-type natriuretic peptide specificity for “systolic HF” - 72% (70-74) [829/1152]
- vi. aminoterminal pro-B-type natriuretic peptide sensitivity for “diastolic HF” - 90% (73-98) [22/24],
- vii. aminoterminal pro-B-type natriuretic peptide specificity for “diastolic HF” - 72% (70-74) [847/1176]

Based on an anticipated response rate of at least 60%, invitations to participate in the study were extended to 2000 people. Participants were randomly selected from the January 2002 electoral roll, using simple random sampling (SPSS 11.0, Chicago, Illinois), to constitute our study population.

3.6 CLINICAL DATA

3.6.1 Clinical examination

A limited clinical examination was conducted by an experienced cardiology nurse. Height and weight were measured without shoes and in light clothing. Body mass index (BMI) was calculated for each participant. Brachial artery systolic and diastolic BP (Korotkoff phase V) were measured to the nearest 2 mmHg on the right arm using a standard mercury sphygmomanometer after 10 minutes of rest in a sedentary position; the measurement was repeated after 5 minutes and the two sets were averaged for each participant.

Prior to the echocardiography assessment and review of the questionnaire, subjects were reviewed by a cardiologist (the author). Participants were asked if they had symptoms of dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea or dependent oedema; and examined for the presence of tachycardia (heart rate >100 beats per minute), raised jugular venous pressure, displaced apex beat, added heart sounds, cardiac murmurs, lung crepitations and peripheral oedema.

3.6.2 Self-administered questionnaire

A self-administered questionnaire was compiled from a number of sources (Appendix A), many of which had been previously validated in an Australian population or were used as a standard by governmental statistical bodies such as the Australian Institute of Health and Welfare and the Australian Bureau of Statistics.

3.6.2.1.1 Evaluation of relevant past medical history

A self-administered questionnaire was used to document a history of myocardial infarction, coronary disease, diabetes and HT. A self-reported history of clinical HF was verified by a review of the subject's medical records.

3.6.2.1.2 Evaluation of lifestyle factors

Questions based on the National Health Survey 2001,²³² a triennial national health questionnaire administered by the Australian Bureau of Statistics, were used to assess levels of alcohol consumption and smoking status. The author sought advice regarding the assessment of physical activity levels in older persons from the staff at the Cardiovascular Disease and Risk Factor Monitoring Unit, Australian Institute of Health and Welfare (contact person: Dr Tim Armstrong). On the basis of their recommendations, physical activity levels over the last week and typical of the last six months were evaluated using the Active Australia survey.²³³ This data will be used as an exposure variable for incident cardiovascular events in the longitudinal analyses, and has not been reported in studies related to this thesis.

3.6.2.1.3 Evaluation of quality of life

A Short Form 36 Health questionnaire was used to estimate quality of life. This tool is widely used, and we administered a version that had been modified for Australian vernacular.

3.6.2.1.4 Evaluation of socioeconomic status

The author sought advice from the Australian Institute of Health and Welfare and the Australian Bureau of Statistics regarding the best methods for determining socioeconomic status in a sample of older Australian adults. Socioeconomic status will be used as an exposure variable for incident cardiovascular events in the longitudinal analyses, and has not been reported in studies related to this thesis.

3.7 CONVENTIONAL ECHOCARDIOGRAPHY

All participants underwent assessment of cardiac structure and function using transthoracic echocardiography (Acuson 128 XP/10, equipped with native tissue harmonic imaging) according to a standardised protocol and according to American Society of Echocardiography recommendations.²³⁴ All measurements were performed off-line and averaged from 3-5 consecutive cardiac cycles.

LV ejection fraction was determined by a modified Simpson's method.²³⁵ LV mass was assessed by the area-length method²³⁶ and indexed to height (LV mass index). LA diameter was obtained from the parasternal long-axis view. LA volume was quantitated using the prolate-ellipsoid and biplane area-length methods.²³⁷ Mitral and aortic valve function was assessed using Doppler and colour-Doppler echocardiography and graded according to previously published criteria.²³⁸ Valvular heart disease was defined as at least moderate stenosis or regurgitation of the mitral and aortic valves.

3.8 ASSESSMENT OF DIASTOLIC FUNCTION

In 2001, when the research presented in this thesis was being planned, contemporary methods for non-invasive identification of DD were based on assessment of transmitral flow during diastole with pulsed wave Doppler.^{121, 123, 239} In particular, Doppler cut-offs for impaired LV relaxation were based on personal communication with the one of the authors of the only other large population-based study of diastolic function that was being proposed at the time. This study from Mayo Clinic was published during the period of our data collection.²⁰ The consistency of Doppler methodology was particularly useful as it facilitated comparisons between our studies.

Pulmonary venous pulsed wave Doppler and tissue Doppler imaging of the mitral annulus was used to distinguish normal from pseudonormal LV filling patterns.¹²³ A description of the data acquisition of these Doppler assessments is included in this

section. A more detailed description of the theory that underscores these echocardiographic techniques is provided in chapter 2. Interpretation of these measures varies according to the studies published in this thesis and will be detailed in Chapters 4 to 9.

3.8.1 Transmitral and pulmonary venous pulsed wave Doppler

Transmitral flow was evaluated for assessment of LV filling and relaxation. The pulsed wave sample volume was placed at the tips of the mitral valve leaflets in the apical 4-chamber view. Transmitral E and A diastolic velocities, E wave deceleration time, A wave duration and isovolumic relaxation time were recorded. The pulmonary venous Doppler profile was assessed as a measure of LA pressure. Maximum velocities of systolic and diastolic pulmonary venous flow; and atrial reversal wave velocities were recorded using a pulsed wave sample volume placed at 1 cm into the right upper pulmonary vein in the apical 4-chamber view. The duration of the atrial reversal wave was also measured and the temporal difference between the durations of transmitral A and pulmonary venous A reversal was calculated.

3.8.2 Mitral annular tissue Doppler velocities

In order to assess mitral annular tissue Doppler velocities, the echocardiography machine settings were optimised to record the high amplitude, low velocity tissue signals. A pulse wave sample size of 2-5 mm was used with high pulse repetition frequency, and a sweep speed of 100 cm/second. Gains were minimized to reduce

spectral broadening of the Doppler signals in order to increase measurement accuracy. Annular velocities during systole, early and late diastole (Sa, Ea and Aa, respectively) were measured at the medial and lateral mitral annulus in the apical 4-chamber view (Figure 3-1). As for all echocardiographic assessments, measurements were performed off-line and averaged from 3 to 5 consecutive cardiac cycles.

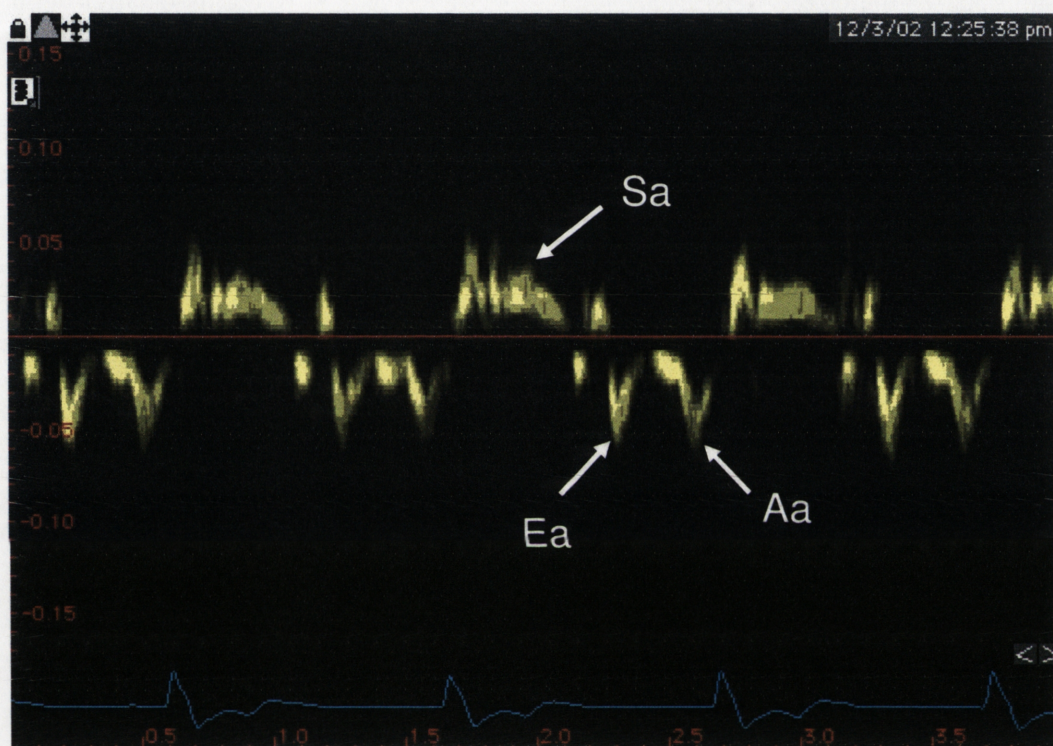


Figure 3-1 Lateral mitral annular pulse wave tissue Doppler velocities

3.8.3 Left atrial size measurement

Measurement of anteroposterior LA linear dimension by M-mode echocardiography^{234, 240} is simple and convenient but not reliably accurate, given that the LA is not a symmetrically shaped three-dimensional (3D) structure.²⁴¹

Furthermore, because LA enlargement may not occur in a uniform fashion,²⁴² one-dimensional assessment is likely to be an insensitive assessment of any change in LA size. In contrast to LA dimension, LA volume by two-dimensional (2D) or 3D echocardiography provides a more accurate and reproducible estimate of LA size, when compared with reference standards such as magnetic resonance imaging (MRI) and cine computerized tomography (CT),²⁴³⁻²⁴⁶ and has a stronger association with cardiovascular outcomes.^{154, 155, 237, 247} Accordingly, the American Society of Echocardiography has recommended quantitation of LA size by biplane 2D echocardiography using either the method of discs (by Simpson's rule) or the area-length method.²⁴⁸ Although we have routinely used the area-length method in our laboratory, we have found that the biplane Simpson's method is comparable in accuracy and reproducibility. Critical elements and common pitfalls for accurate and reproducible measurement of bi-plane LA volume assessment are outlined in Table 3-1. Echocardiographic methods systematically underestimate LA volume when compared with CT²⁴⁹ or MRI quantitation²⁴⁵, which in turn underestimates true LA size²⁵⁰. More recently, magnetic electroanatomic mapping has also been used for assessment of LA volume.²⁵¹ However, because of its portability and safety, echocardiographic assessment of LA volume is preferable to other imaging methods in clinical practice.

Table 3-1 Critical elements for accurate measurement and interpretation of maximum left atrial volume

Step	Common Limitations/Errors	Suggestions
A. Optimize LA image quality	Atria are located in the far field of the apical views. Reduction of lateral resolution may result in apparently thicker LA walls.	Not improved by modifying the gain settings: Increase in gain will further reduce LA lumen size Decrease in gain may lead to image "drop out" and difficulties in planimetry of LA area Use high resolution sample box to increase pixel density and facilitate accurate tracing of the endocardial border Capture at least five beats for each cine loop to maximize likelihood of obtaining adequate image quality
B. Obtain maximal LA size	LA is foreshortened	Modify transducer angulation or location (place the transducer one intercostal space lower) until LA image is optimized and not foreshortened If discrepancy in the two lengths measured from the orthogonal planes is >5 mm, acquisition should be repeated until the discrepancy is reduced
C. Timing of maximum LA size	Correct frame for measurement is not selected	Choose frame just before mitral valve opening
D. LA area planimetry	LA border is inconsistently defined	Consistently adhere to convention: Inferior LA border—plane of mitral annulus (not the tip of leaflets) Exclude atrial appendage and confluences of pulmonary veins
E. Long-axis LA length	LA long axis is inconsistently delineated	Consistently adhere to convention: Inferior margin—midpoint of mitral annulus plane Superior (posterior) margin—midpoint of posterior LA wall
F. Interpretation	Qualitative categorization of LA size	LA volume indexed to body surface area is optimally interpreted as a continuous variable (using a reference point of 22 ± 5 ml/m ² as "normal")

From Abhayaratna et al.²⁵²

3.9 12-LEAD ELECTROCARDIOGRAM

All 12-lead electrocardiograms were assessed independently by two cardiologists (the author and Dr Nikolic) without knowledge of the results of the clinical and echocardiographic assessments.

3.10 SEROLOGICAL TESTS

3.10.1 Routine blood test

Venous blood was taken after an overnight fast of between 8-12 hours. Using standardised methods that are applied in the clinical setting (ACT Pathology), fasting glucose and lipids, full blood count and renal function were assessed.

3.10.2 Aminoterminal pro-B-type natriuretic peptide

Venous blood was collected in serum tubes, centrifuged and stored at -70°C until batch analysis. NT-proBNP levels were measured using a commercially available and fully automated electrochemiluminescence sandwich immunoassay on an Elecsys 1010 (proBNP®, Roche Diagnostics).

3.11 PULSE WAVE ASSESSMENT OF ARTERIAL STIFFNESS

PWV was assessed noninvasively using the Sphygmocor system (AtCor Medical, Sydney, Australia) on the day of the echocardiography assessment and after an overnight fast. Electrocardiogram-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was estimated using surface measurements (Figure 3-2). Carotid-femoral transit time was estimated in 8–10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. PWV was calculated as the carotid-femoral path length divided by the carotid-femoral transit time.

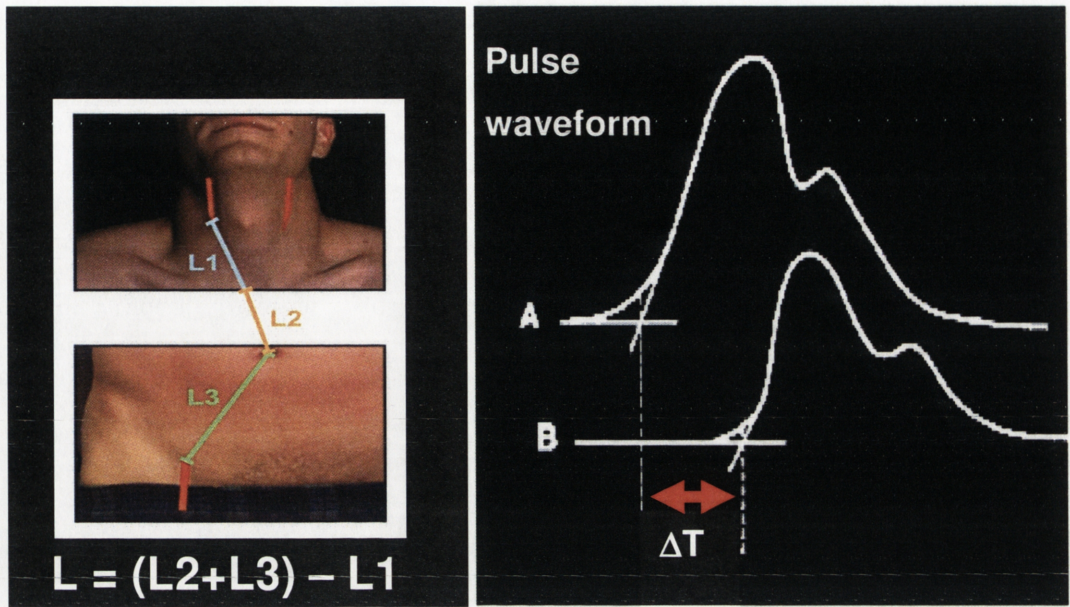


Figure 3-2 Measurement of carotid-femoral pulse wave velocity by applanation tonometry

Left panel - Path length is calculated using the following surface measurements: sternal notch to carotid pulse (L1); sternal notch to umbilicus (L2); and umbilicus to femoral pulse (L3). Transit length (L) = (L2+L3)-L1. Right panel - Transit time is calculated as the time difference (ΔT) between (A) the R wave on the electrocardiogram to the foot of the carotid artery pulse wave; and (B) the R wave on the electrocardiogram to the foot of the femoral artery pulse wave. We have used the intersecting tangent method to identify the foot of respective waveforms. Carotid-femoral pulse wave velocity is calculated as the path length (L) divided by the transit time (ΔT).

3.12 DATA HANDLING AND MONITORING

Data was collected on formatted sheets (questionnaires, clinical examination findings, and biological testing results) and later entered into computer databases. Multiple, linked databases were developed using Microsoft Access. The databases were set up with data cleaning facilities including range checks, skips and logical checks. A random sample of participant details (5%) required double entry to quantify errors in data entry. Checks on outliers also made to assess errors in data entry.

3.13 REPRODUCIBILITY AND RELIABILITY OF STUDY ASSESSMENTS

Echocardiographic measurements were performed off-line and averaged from 3 to 5 consecutive cardiac cycles in order to minimize biological and intra-observer variations, and obtain a more representative evaluation of each individual. Intra- (the author) and inter-observer variability (the author and Dr Tom Marwick) were formally assessed using a sample of 50 subjects. The results are reported in Chapter 4 as an inter-class variation, reflecting the fact that assessment of LV function is classified as ordinal categories for clinical purposes. Accordingly, this approach was used in the original research papers (Chapters 4 to 9, inclusively). Test-retest variability was assessed in 30 subjects in a separate assessment after a period of 1-36 hours after the original study assessment.

The commercial immunoassay for NT-proBNP on the Elecsys 1010 platform has a within run coefficient of variability (CV) of 0.7-1.6% and a between run CV of 5.3-

6.7%,²⁵³ and this has been verified with in-house testing in clinical laboratories (ACT Pathology and Mayo Clinic, Rochester).

At least three separate pulse wave assessments (with each assessment consisting of 8-10 sequential radial, carotid and femoral waveforms) were conducted for each subject using the Sphygmocor system, and the average was recorded. The commercial software (AtCor Medical, Sydney, Australia) has internal quality checks based on pulse waveform variability (timing, amplitude and intensity) and the standard deviation of PWV measurement. Only high quality data were included in our analyses.

3.14 POTENTIAL SOURCES OF BIAS

3.14.1 Sampling bias

Sampling bias refers to the systematic error introduced with the use of an inappropriate sampling frame, from which sections of the target population are over- or under-estimated, with extreme bias occurring if there is zero probability of being selected. For example, there are a number of studies have purported to be population-based when their sampling frame is a medical registry. Obviously, this would exclude subjects who were too healthy (or were unwilling) to seek medical attention during the period of the study. Such a bias affects the external validity of the study, i.e. the generalisability of the study.

The study was restricted to residents of the Southern Districts of the Australian Capital Territory (South Canberra, Woden Valley, Weston Creek and Tuggeranong).

There were a number of benefits to this approach that would potentially improve response rates and facilitate ascertainment of exposure/outcome status. First, the assessment clinic was based in Canberra Hospital, which has an established rapport with the communities in the Southern Districts. Second, residents in the southern districts of the Australian Capital Territory are generally admitted to Canberra Hospital for cardiovascular events, and their medical records could be accessed by the author and research assistants to verify self-reported comorbidities. In contrast, there were no identifiable disadvantages that would potentially impact on the internal or external validity of the study. The health and socioeconomic characteristics of the Southern and Northern Districts of the ACT are not considered to be different, and accordingly the study could be generalised to the ACT population aged over 60 years. Indeed, one of the major benefits of conducting a population-based survey, particularly one that had a good participation rate, was the ability to generalise our results to populations of age over 60 years in Australia and most developed countries with similar racial/ethnic constitutions. Additionally, the characteristics of Canberra's urban infrastructure and the fact that Canberra Hospital has no specific subspecialty services would make it highly unlikely that a patient with cardiovascular disease would choose to live close in proximity to the hospital. If this were the case, rates of cardiovascular disease would over-represent true prevalence in the community.

In the Canberra Heart Study, our sampling frame was the electoral roll (January 2002). Obviously, the sampling frame would exclude those that were not eligible to vote because of residency status or were too incapacitated to vote due to cognitive

deficits. Because of the known relationship between cardiovascular disease and cognition,²⁰² the latter group would be expected to have a high atherosclerotic burden and therefore a relatively high prevalence of left ventricular dysfunction. However, this issue would have little effect on our results as subjects with such cognitive deficits would have been unable to provide informed consent to participate in our study had they been included in the sampling frame. A more important concern with the use of the electoral roll as a sampling frame was the accuracy of the electoral roll. To an extent, we were fortunate that our recruitment efforts commenced shortly after Federal and Territory elections. As a result the electoral roll had been updated by the voting public through the Australian Electoral Commission registry in preparation for the elections.

A number of factors related to our study population may limit the generalisability of our results to other populations. First, the vast majority of the study population of Canberra residents was White (97.6%) and our results may not be applicable to non-White populations. Second, the National Health Survey has documented that ACT residents have lower rates of classical risk factors for cardiovascular disease,²⁵⁴ which may decrease the prevalence of HF and left ventricular dysfunction in this population compared to national rates. On the other hand, ready access to medical therapy for acute coronary syndromes and HT in this urban setting may paradoxically increase the prevalence of structural heart disease and HF, through a survivor effect.

3.14.2 Selection bias

Selection bias refers to the systematic error introduced when access to the study population varies across different exposure-disease subgroups. Such a bias affects the internal validity of the study, which may result in an incorrect estimate of the true disease prevalence in the sample population and a distortion of the strength and/or direction of exposure-disease relationships in the study.

We extended invitations to 2000 subjects selected as a simple random sample of 18,000 Canberra residents of age 60-85 years. A comparison of demographic characteristics of the sampling frame and (Chapter 4) and the study population confirmed that our random sampling method was successful in the selection of a representative sample of the population, at least with regard to age and gender. It would also be unlikely that our sampling process would systematically promote differential access to the study population for different exposure-disease subgroups

In a cross-sectional survey, the major source of selection bias is a poor participation rate. In general, a participation rate over 70% is required to avoid major concerns regarding the potential for selection bias. In the Canberra Heart Study, seventy-five percent (1388/1846) of the eligible subjects agreed to participate in the survey. The only groups with participation rates under 70% were women aged 75-79 years (68%) and over 80 years (49%). As older women were under-represented in our sample, there may be an underestimation of disease prevalence in the source population of community-dwelling adults aged 60-86 years.

In order to explore the possibility of a differential participation in patients with various exposure-disease states, we assessed hospital medical records to collect

limited clinical data on cardiovascular disease status in a random sample of 100 non-participants. There was no significant difference between participants and non-participants with regards to rates of exposures such as HT, diabetes mellitus; or disease states such as HF, atrial fibrillation, or myocardial infraction.

Despite obvious limitation of such analyses on non-participants, these findings would suggest that there is little evidence that non-participation in the Canberra Heart Study has introduced a selection bias.

3.14.3 Information bias

Information bias results from systematic differences in the manner in which exposure or outcome data are collected from the various study groups. Such a bias also adversely affects the internal validity of the study.

During the clinic assessment, the order of data gathering by the author was chosen to minimize potential for information (observation) bias. Specifically, a clinical examination was performed by a cardiologist (the author) prior to echocardiographic assessment or the review of either the self-administered questionnaire that detailed past medical history or the BP measurements performed by study nurses. This approach, in addition to the routine application of objective criteria for exposure and outcome variables, facilitated the blinding of evaluations of both exposure and outcome variables in order to minimise diagnostic and exposure suspicion bias.

Another source of information bias is recall bias, which occurs when individuals with particular adverse health outcomes report their previous exposures differently from

those without illness; or when those exposed to a potential hazard report subsequent events with a differing degree of accuracy or completeness. In our study, we have measured the majority of exposure variables biochemically and clinically, and checked medical records to confirm self-reported clinical exposures and outcomes. Thus our classification of exposure and outcome status was independent of subject recall and often based on objective biological measurements.

3.15 APPROVAL BY HUMAN RESEARCH ETHICS COMMITTEE

This project represents a cross-sectional observational study without a proposed intervention. Only individuals who volunteered to participate in the study and provided informed consent were recruited into the study. The project provided a low level of intrusion. The study was conducted according to the principles stated by the Helsinki declaration and complied with the recommendations of the NHMRC 1992 Supplementary Notes 7, *Guidelines for Good Clinical Research Practice*, and *Guidelines for the Protection of Privacy in the Conduct of Medical Research*.

The two major ethical issues to be considered during this research were:

- i. safety and tolerability of diagnostic procedures
- ii. confidentiality

A 10-mL sample of blood was withdrawn from each study participant. As anticipated, the procedure caused minimal discomfort without exception. Regardless, each participant was offered an anaesthetic cream (EMLA) prior to venesection. All

other diagnostic procedures included in the study were non-invasive and were considered to be extremely safe and indeed were well tolerated.

To ensure adequate confidentiality, individual identification details were stored in a locked filing cabinet in a room that was locked after hours. Research records were entered on a computer database with only numerical identifiers.

Each participant was provided a copy of the biological test results. At the participant's request, a copy was forwarded to their nominated medical practitioner(s). As part of an implicit "duty of care", any abnormal results were highlighted, and the participant was referred to their general practitioner for appropriate medical follow-up.

The research protocol was reviewed and approved by the Human Research Ethics Committees of ACT Health and the Australian National University. As part of the study protocol, approval was granted to assess hospital medical records to collect limited data on cardiovascular disease status on a random sample of 100 non-participants.

Chapter 4: PREVALENCE OF HEART FAILURE AND SYSTOLIC VENTRICULAR DYSFUNCTION IN OLDER ADULTS

Published in part in:

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Prevalence of heart failure and systolic ventricular dysfunction in older Australians:
the Canberra Heart Study. *Med J Aust* 2006;184:151-154

4.1 ABSTRACT

Objective. To estimate the prevalence of heart failure (HF) and left ventricular (LV) systolic dysfunction in older Australians.

Design, Setting, Participants. A cross-sectional survey of 1275 randomly selected residents of Canberra (participation rate 75%), aged 60 to 86 years (mean age 69.4; 50% men), conducted between February 2002 and June 2003.

Main Outcome Measures. Age/gender-specific prevalence rates of clinical HF and LV systolic dysfunction, defined as a LV ejection fraction $\leq 50\%$.

Results. In the study sample, 72 subjects [5.6%; 95% confidence interval (CI) 4.4%-7.1%] had clinical HF that had been previously diagnosed and confirmed by our assessment. A further 0.6% (95%CI 0.3%-1.2%) had evidence of structural heart disease and symptoms/signs of cardiac insufficiency without a previous diagnosis of clinical HF (i.e. undiagnosed clinical HF). Thus, overall the prevalence of clinical HF in the sample was 6.3% (95%CI 5.0%-7.7%). Clinical HF increased in prevalence with advancing age (4-fold increase in prevalence from 60-64 to 80-86 years, $p < 0.0001$). Of the 75 subjects (5.9%; 95%CI 4.7%-7.3%) with LV systolic dysfunction, 44 (59%) were in the preclinical stage of disease.

Conclusions. Diagnosed HF cases represent the “tip of the iceberg” for the national burden of HF and LV systolic dysfunction. Clinically identifiable HF cases can remain undiagnosed, and the majority of subjects with LV systolic dysfunction are preclinical.

4.2 BACKGROUND

The human and economic burden of heart failure (HF) in the community is expected to increase with our ageing population. Even with the availability of effective medical therapy, the syndrome of HF is associated with substantial mortality, morbidity and economic cost (estimated to be over AUD\$1,000 million in 2000).²⁵⁵ Although HF, under the umbrella of 'cardiovascular disease', has been nominated as a National Health Priority Area,²⁵⁶ there are no population-based data with which to estimate the prevalence and incidence of HF and left ventricular (LV) dysfunction in Australia.²⁷ Such information is important to guide the allocation of health resources for managing HF and monitoring the impact of therapeutic and preventive strategies over time.

The aim of this study was to determine the prevalence of HF and LV systolic dysfunction in a population-based sample of older Australians.

4.3 METHODS

4.3.1 Study sample

Two thousand residents of Southern Canberra, aged 60-85 were randomly selected from the January 2002 electoral roll, and invited by letter to participate in a cross-sectional echocardiographic survey. Institutionalised subjects and those who had died or had moved away from the Territory were excluded from the study sample (n=154). Participants were enrolled between February 2002 and June 2003. The sample size was selected based on precision of estimates to determine a prevalence of LV systolic dysfunction of 4% and the assumption of a 60% participation rate.

4.3.2 Echocardiographic assessment

Cardiac structure and function were assessed in all participants using transthoracic echocardiography (Acuson 128 XP/10, Siemens, Mountain View, Calif, USA) according to a standardised protocol.

Abnormal LV diastolic function was graded into three categories using Doppler evaluation of mitral and pulmonary venous inflow and tissue Doppler imaging of lateral mitral annulus motion (abnormal relaxation filling pattern: mild DD; pseudonormal filling pattern: moderate LV diastolic dysfunction; restrictive filling pattern: severe LV diastolic dysfunction).²⁵⁷

LV mass was assessed by the area-length method²³⁶ and indexed to height. Sex-specific reference limits (97.5th percentiles) were derived from the frequency distribution of indexed LV mass in a reference sample of subjects who had no history of ischaemic heart disease, hypertension, diabetes, atrial fibrillation or more than mild valvular heart disease and who were not taking cardioactive medications. Increased indexed LV mass was defined as > 132 g/m for women and > 157 g/m for men.

Mitral and aortic valvular function was assessed using Doppler and colour-Doppler echocardiography and graded according to previously published criteria.²³⁸ Valvular heart disease was defined as at least moderate stenosis or regurgitation of the mitral and/or aortic valves. Structural heart disease was defined as LV systolic dysfunction, moderate or severe LV DD, increased indexed LV mass and/or valvular heart disease.

4.3.3 Ascertainment of heart failure clinical status

A self-reported history of clinical HF was verified by a review of the subject's medical records. During a consultation with a cardiologist who was blinded to the echocardiography findings and past medical history, participants were asked if they had symptoms of dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea or dependent oedema. They were examined for the presence of increased heart rate, raised jugular venous pressure, displaced apex beat, added heart sounds, cardiac murmurs, lung crepitations or peripheral oedema. HF clinical status was ascertained according to the Framingham criteria for the clinical diagnosis of HF.²⁵⁸ Subjects with LV systolic dysfunction but no past history or clinical evidence of HF were considered to be in the preclinical phase of disease.

4.3.4 Evaluation of clinical predictors of preclinical LV systolic dysfunction

A self-administered questionnaire was used to document a history of myocardial infarction, coronary disease, diabetes, HT and alcohol consumption levels (none; low-risk; high-risk [the latter defined as ≥ 140 g/week for women and ≥ 280 g/week for men]²⁵⁹).

Brachial artery systolic and diastolic BP (Korotkoff phase V) were measured to the nearest 2 mmHg on the right arm using a standard mercury sphygmomanometer after 10 minutes of rest in a sedentary position. The measurement was repeated after 5

minutes and the two sets were averaged for each participant. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or the use of medical therapy for HT.

Diabetes was defined as a fasting serum glucose level ≥ 7 mmol/L or the use of insulin or oral hypoglycaemic agents. Height and weight were measured without shoes and in light clothing.

Body mass index (BMI) was calculated for each participant and categorised using the World Health Organisation classification scheme (not overweight or obese < 25 kg/m², overweight 25.0 to 29.9 kg/m², obese ≥ 30 kg/m²).

4.3.5 Statistical analysis

Prevalence rates of LV systolic dysfunction and clinical HF were determined and stratified according to age and sex. The associations between clinical parameters and preclinical LV systolic dysfunction were examined using χ^2 tests and in multivariable analyses using logistic regression to adjust for age and gender.

4.3.6 Ethics approval

Our study was approved by the human research ethics committees of ACT Health and the Australian National University.

4.4 RESULTS

4.4.1 Participation rates

Seventy-five percent (1388/1846) of the eligible subjects agreed to participate in the survey, including subjects of age 86 years who celebrated their birthday during the period between their acceptance to participate in the study and their attendance at the assessment clinic. All participants provided written and informed consent. The only groups with participation rates under 70% were women aged 75-79 years (68%) and over 80 years (49%). Consequently, compared to the source population, the sample population had a higher proportion of men (50.5% versus 47.2%, $p<0.012$) and were younger (68.9 years vs. 69.6 years, $p=0.0005$). Approximately 92% of participants (1275/1388; mean age 69.4; 50% men) completed all the investigations relevant to this study.

4.4.2 Prevalence rates of LV systolic dysfunction

Overall, 269 subjects (21.1%; 95%CI 18.8-24.4%) had evidence of structural heart disease; 75 (5.9%, 95%CI 4.7%-7.3%) with LV systolic dysfunction; 72 (5.6%) with moderate or severe diastolic function and EF >50%; 102 (8%) with increased LV mass without impaired systolic function or moderate/severe diastolic function; and 20 (1.6%) with aortic and mitral valvular heart disease.

Age/gender-specific rates of clinical HF and LV systolic dysfunction are presented in Table 4-1.

Table 4-1 Age/gender-specific prevalence of clinical heart failure and LV systolic dysfunction.

Subjects Affected, n (%)						
Age Group, years						
	60-64	65-69	70-74	75-79	80-86	All
Clinical Heart Failure						
Men	7 (3.6)	12 (7.3)	6 (5.2)	16 (17.8)	11 (15.7)	52 (8.2)
Women	5 (2.6)	3 (2.0)	7 (4.8)	8 (7.8)	5 (10.4)	28 (4.4)
All	12 (3.1)	15 (4.8)	13 (5.0)	24 (12.4)	16 (13.6)	80 (6.3)
LV Systolic Dysfunction						
<u>Any, ejection fraction $\leq 50\%$</u>						
Men	11 (5.6)	13 (7.9)	10 (8.6)	9 (10)	12 (17.1)	55 (8.7)
Women	4 (2.1)	3 (2.0)	5 (3.4)	3 (2.9)	5 (10.4)	20 (3.1)
All	15 (3.9)	16 (5.1)	15 (5.7)	12 (6.2)	17 (14.4)	75 (5.9)
<u>Moderate or Severe, ejection fraction $\leq 40\%$</u>						
Men	3 (1.5)	6 (3.7)	3 (2.6)	6 (6.7)	3 (4.3)	21 (3.3)
Women	2 (1.0)	0 (0.0)	1 (0.7)	1 (1.0)	2 (4.2)	6 (0.9)
All	5 (1.3)	6 (1.9)	4 (1.5)	7 (3.6)	5 (4.2)	27 (2.1)

Of those with any LV systolic dysfunction, 44 (59%) were preclinical. However, only 6 of the 27 subjects (22%) with moderate or severe LV systolic dysfunction were preclinical.

4.4.3 Clinical correlates of preclinical LV systolic dysfunction

Increasing age, male gender and a history of myocardial infarction were associated with preclinical LV systolic dysfunction (Table 4- 2).

Table 4-2 Associations between clinical characteristics and preclinical LV systolic dysfunction

	Unadjusted Odds Ratio	Adjusted Odds Ratio*
Men	2.3 (1.2-4.4)	2.3 (1.2-4.4)†
Age group (referent: 60-69 years)		
70-79 years	1.2 (0.6-2.4)	1.3 (0.6-2.5)‡
80-86 years	3.2 (1.4-7.2)	3.0 (1.3-6.9)‡
Hypertension	1.2 (0.6-2.1)	1.1 (0.6-2.0)
Diabetes	0.3 (0.1-1.2)	0.3 (0.1-1.1)
Myocardial infarction	3.9 (1.6-9.7)	3.0 (1.2-7.5)
Coronary disease	2.1 (1.03-4.2)	1.6 (0.8-3.3)
Body mass index (referent: <25 kg/m ²)		
25-29.9 kg/m ²	0.6 (0.3-1.2)	0.5 (0.3-1.1)
≥30 kg/m ²	0.7 (0.3-1.5)	0.8 (0.3-1.6)
High-risk alcohol intake	1.0 (0.2-4.4)	1.0 (0.2-4.4)

**adjusted for age and gender unless specified; †adjusted for age; ‡adjusted for gender*

Although diabetes was associated with prevalent clinical systolic dysfunction (OR 2.6; 95%CI 1.2-5.7), there was a trend toward a lower likelihood of preclinical LV systolic dysfunction in diabetics (OR 0.26; 95%CI 0.1-1.1). In this cross-sectional analysis, there were no significant associations between preclinical LV systolic dysfunction and hypertension, body mass index category or alcohol intake status.

4.4.4 Clinical heart failure

Of the study sample, 72 subjects (5.6%; 95%CI 4.4%-7.1%) had clinical HF that had been previously diagnosed and validated by our assessment. Approximately 60% of subjects with diagnosed HF had preserved LV systolic function (EF>50%), a finding that was more frequent in women with diagnosed HF (77% vs. 52%, $p=0.039$). A further 8 participants (0.6%; 95%CI 0.3%-1.2%) without a previous diagnosis of clinical HF had evidence of structural heart disease and symptoms/signs of cardiac insufficiency (i.e. undiagnosed clinical HF). Thus overall, the prevalence of clinical HF in the sample was 6.3% (95%CI 5.0%-7.7%). Clinical HF was more common in men (8.2% vs. 4.4%, $p=0.005$) and increased in frequency with advancing age (4.4-fold increase in prevalence from 60-64 to 80-86 years, $p<0.0001$). The proportion of undiagnosed clinical HF cases was not related to age ($p=0.34$) or gender ($p=0.54$).

4.5 DISCUSSION

The Canberra Heart Study provides the first population-based estimates of HF prevalence in Australia. Prior estimates of HF prevalence and incidence have been derived from extrapolation of overseas data,²⁶⁰ hospital separations, or studies on clinic-based samples in which a minority had echocardiographic confirmation of underlying structural heart disease.²⁶¹ Our results illustrate that diagnosed HF cases represent the “tip of the iceberg” for the national burden of HF and structural heart disease. Clinically identifiable HF cases can remain undiagnosed, and although 21.1% of our sample of older Australians had structural heart disease, only 6.3% had

clinical HF. Moreover, of the 5.9% of the study population with LV systolic dysfunction, 59% were in the preclinical stage of disease.

4.5.1 Comparison with international studies

Comparison of our findings with international studies is limited by differences in study methodology and outcome definitions. Framingham investigators have reported that approximately 6% to 10% of the population aged over 65 experience clinical HF²⁶². However, in such early epidemiological cardiovascular surveys, HF status was ascertained using clinical scores that had relatively poor sensitivity and specificity for structural heart disease. It has only been during the last decade that surveys have incorporated echocardiography to confirm structural heart disease in subject with non-specific symptoms and signs of cardiac insufficiency. The burden of LV systolic dysfunction in our sample is consistent with estimates from the Olmsted County²⁰, Rotterdam²¹ and ECHOES⁹³ surveys, conducted in predominantly Caucasian populations with similar cardiovascular risk profiles (Table 4-3). However, our prevalence rates of LV systolic dysfunction are lower than the estimates from the Strong study⁹⁵, conducted exclusively in a population of Native Americans, and the Glasgow study²⁶³, whose population has a high prevalence of cardiovascular disease. Like the surveys from the United States

Table 4-3 Comparison of results from prevalence survey of LV systolic dysfunction

Study	Sample size (% men)	Mean age in years (range)	Participation rate	Identification of congestive heart failure	Method of measuring EF	Definition of abnormal LV systolic function	Prevalence (%)
Glasgow	1467 (48)	50 (25-75)	56%*	MRC dyspnoea class; use of diuretics	2D	EF < 35%	7.7
Rotterdam	2267 (45)	66 (55-94)	78%	Two-step approach based on (i) WHO dyspnoea class; clinical examination; (ii) indication for cardiac medications	M-mode	EF < 42.5%	3.7
Olmsted County	2042 (48)	63 (45-96)	47%	Medical records	M-mode, 2D, and visual estimate	EF ≤ 50%	6.0
Strong Heart	3184 (37)	58 (49-78)	62%	Unspecified	M-mode	EF ≤ 40%	2.0
						EF ≤ 54%	13.9
						EF < 40%	2.9
ECHOES	3960 (50)	61 (≥ 45)	63%	New York Heart Association classification	2D	EF ≤ 50%	5.3
						EF < 40%	1.8
Canberra†	1275 (50)	69 (60-86)	75%	Medical records and clinical examination	2D	EF ≤ 50%	5.9
						EF ≤ 40%	2.1

and Northern Europe,^{20, 21, 93, 95, 263} we have documented that most community cases of LV systolic dysfunction are preclinical.

4.5.2 Limitations

Although our population-based sample and good participation rate reduce selection bias and strengthen the validity of this study, a number of factors may limit generalisability of our results. First, we have identified that older women, due to their lower participation rate, were under-represented in our sample. This may result in an underestimation of disease prevalence in the source population of community-dwelling adults aged 60-86 years. Second, the vast majority of the study population was Caucasian (97.6%) and our results may not be applicable to non-Caucasian populations. Third, the National Health Survey has documented that ACT residents have lower rates of classical risk factors for cardiovascular disease,²⁵⁴ which may decrease the prevalence of HF in this population compared to national rates. On the other hand, ready access to medical therapy for acute coronary syndromes and HT in this urban setting may paradoxically increase the prevalence of structural heart disease and HF, through a survivor effect.

4.5.3 Implications

Our results have several important public health implications. Firstly, with the availability of efficacious medical therapy for patients with clinical HF, it is crucial

to optimise methods of diagnosing the condition in the community. Using strict criteria for the clinical diagnosis of congestive HF, we found that 10% of the subjects with structural heart disease and clinical evidence of HF had not been previously diagnosed with the condition. The National Institute of Clinical Studies has recently evaluated barriers to the correct diagnosis of HF and the implementation of proven management strategies in primary care.²⁶⁴ Solutions based on targeted education of health professionals and patients, and the increased use of diagnostic tools such as echocardiography, have been proposed.

Secondly, since secondary preventive measures have been shown to be effective for patients with preclinical LV systolic dysfunction, methods for identifying affected patients should also be optimised. Targeted screening programs of high-risk subjects (as identified in this study: men, older age groups, patients with prior documented coronary disease or myocardial infarction) should be evaluated for their cost-effectiveness.

Thirdly, with the anticipated increase in the proportion of the population of age over 60 years (among whom most HF cases arise) and escalating rates of obesity and diabetes in the community, there seems little hope to stem the rise in HF cases to epidemic proportions unless primary preventive efforts directed at the individual and population level are adopted.

Chapter 5:

CHARACTERISTICS OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN THE COMMUNITY

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Heart 26;92:1259-64

5.1 ABSTRACT

Objective. To determine the prevalence and predictors of left ventricular (LV) diastolic dysfunction in older adults.

Design, Setting, Participants. A cross-sectional survey of 1275 randomly selected residents of Canberra (participation rate 75%), aged 60 to 86 years (mean age 69.4; 50% men), conducted between February 2002 and June 2003.

Main Outcome Measures. Prevalence rates of LV diastolic dysfunction as characterised using comprehensive Doppler echocardiography.

Results. The prevalence of any diastolic dysfunction was 35.6% (95% confidence interval [CI] 32.9%-38.3%) and moderate-severe diastolic dysfunction was 7.5% (95%CI 6.1%-9.1%). Of those with moderate-severe diastolic dysfunction, 84.7% had a LV ejection fraction (EF) $\geq 50\%$ and 77.2% were preclinical. Predictors of diastolic dysfunction included increasing age ($p < 0.0001$), reduced EF ($p < 0.0001$), obesity ($p < 0.0001$); history of HT ($p < 0.0001$), diabetes ($p = 0.02$) and myocardial infarction ($p = 0.003$). Moderate-severe diastolic dysfunction with normal EF, although predominantly preclinical, was independently associated with increased LV mass ($p < 0.0001$), LA volume ($p < 0.0001$), circulating aminoterminal pro-B-type natriuretic peptide levels ($p < 0.0001$), and decreased quality of life ($p < 0.005$).

Conclusion. Diastolic dysfunction is common in the community and frequently unaccompanied by overt HF. Despite the lack of symptoms, advanced diastolic dysfunction with normal EF is associated with reduced quality of life and structural abnormalities that reflect increased cardiovascular risk.

5.2 BACKGROUND

Over the past decade, several important observations on the pathophysiological mechanisms underlying HF in the community have been documented through population-based echocardiographic surveys.^{20, 21, 58, 59, 93, 95, 263, 265} Firstly, HF has been reported in the presence of a normal EF.^{58, 265} Although controversial, the presumed pathophysiology for most patients with HF and a normal EF is DD.^{61, 73} Secondly, subjects with HF and a normal EF have been shown to have a poor prognosis, even though mortality and morbidity in this group are not as high as in patients with a reduced EF.^{94, 265}

Following these observations, interest in the epidemiology of DD has been growing, which has been facilitated by the availability of non-invasive Doppler methods of characterising diastolic function.¹²³ A recent study²⁰ showed that subjects with normal EF can have moderate or severe DD, most often without accompanying clinical evidence of HF. The validity of findings from these cross-sectional surveys of DD has, however, been compromised by low participation rates²⁰ and the failure to use comprehensive Doppler methods²⁵⁷ to distinguish subjects with normal and pseudonormal mitral inflow patterns, which have increased the potential for selection bias and misclassification of diastolic function. In addition, there is a paucity of data regarding echocardiographic and clinical characteristics of subjects with DD and normal EF (DD-NEF) and their influence on clinical status. Our objectives in this study were to determine the prevalence of DD in older adults and to describe the clinical spectrum of subjects with DD-NEF.

5.3 METHODS

5.3.1 Study population

Using simple random sampling from a population register (Federal electoral roll, January 2002), 2000 Canberra residents, aged 60-85, were selected to constitute our study population. Subjects were invited to participate by letter. Institutionalised subjects and those who had died or had moved away from the Territory were excluded from the study sample. All study participants provided written and informed consent for the study investigations, and were enrolled between February 2002 and June 2003.

5.3.2 Assessment of clinical risk factors for heart failure

A self-administered questionnaire was used to gather data on a history of myocardial infarction, angina, HT or diabetes. Brachial artery systolic and diastolic BP was measured after 10 minutes of rest in a seated position; two sets were averaged for each participant. Height and weight were measured without shoes and in light clothing. Body mass index was calculated for each participant (weight in kilograms divided by the square of height measured in metres) and categorised using the World Health Organisation classification scheme (not overweight or obese $<25 \text{ kg/m}^2$, overweight 25.0 to 29.9 kg/m^2 , obese $\geq 30 \text{ kg/m}^2$).

5.3.3 Echocardiography

One of two experienced sonographers assessed cardiac structure and function by using transthoracic echocardiography (Acuson 128 XP/10, equipped with native tissue harmonic imaging technology) according to a standardised protocol. Measurements were made online and recorded on tape with participants' initials and study number as their only identification. A cardiologist, blinded to the participant's clinical data, interpreted the echocardiogram after review off line. LV EF was quantified by the biplane disc summation method (Simpson's rule) on the two-dimensional echocardiographic images from the apical four- and two-chamber views.²⁶⁶ LV systolic function was categorised according to EF ($\leq 40\%$, 41–50%, $> 50\%$) and the presence of regional LV wall motion abnormalities. LV diastolic function was graded into four categories by Doppler evaluation of the mitral and pulmonary venous inflow and by tissue Doppler imaging of the lateral mitral annulus motion (Table 5-1).²⁵⁷ In a stratified subsample of 50 participants, interobserver reproducibility for grading of systolic and diastolic function was very good ($\kappa_{\text{systolic}} = 0.88$, 95% confidence interval (CI) 0.63 to 1.0 and $\kappa_{\text{diastolic}} = 0.89$, 95% CI 0.64 to 1.0). Valvular heart disease was defined as at least moderate stenosis or regurgitation of the aortic or mitral valve on colour Doppler and quantitative Doppler echocardiographic evaluation. LV mass was assessed by the area-length method, by using the two-dimensional short-axis parasternal view at the papillary muscle level to measure LV muscle area and the apical four-chamber view to measure the LV length.²³⁵ The LV mass was indexed for each participant's body surface area. Maximum LA volume was quantified by the biplane Simpson method¹⁵⁴ and indexed for body surface area.

Table 5-1 Doppler Assessment of left ventricular diastolic function

	Mitral inflow	Pulmonary venous inflow	TDI MAM
Normal	$0.75 < E/A < 1.5$ $DT > 160\text{ms}$	$S > D$ $MV\text{ Adur} > PV\text{ Adur}$	$E/e' < 10$
Mild LV diastolic dysfunction	$E/A < 0.75$ $DT > 240\text{ms}$	$S > D$ $MV\text{ Adur} > PV\text{ Adur}$	$E/e' < 10$
Moderate LV diastolic dysfunction	$0.75 < E/A < 1.5$ $DT > 160\text{ms}$	$S < D$ $MV\text{ Adur} + 30\text{ms} < PV\text{ Adur}$	$E/e' \geq 10$
Severe LV diastolic dysfunction	> 1.5 $DT < 160\text{ms}$	$S < D$ $MV\text{ Adur} + 30\text{ms} < PV\text{ Adur}$	$E/e' \geq 10$

At least 2 Doppler criteria consistent with moderate-severe LVDD were required to distinguish from normal diastolic function. E, peak early mitral inflow filling velocity; A, peak mitral filling velocity at atrial contraction; DT, deceleration time of mitral E wave; MV Adur, duration of mitral A wave; S, peak velocity of pulmonary venous forward flow during systole; D, peak velocity of pulmonary venous forward flow during diastole; PV Adur, duration of pulmonary venous reversal wave at atrial contraction; e', peak velocity of lateral mitral annulus motion during early diastole. TDI MAM = Tissue Doppler imaging of mitral annular motion

5.3.4 Ascertainment of heart failure status

A self-reported history of clinical HF was verified by a review of the subject’s medical records. During a consultation with a cardiologist who was blinded to the echocardiographic findings and medical history, participants were asked if they had

symptoms of dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea or dependent oedema. They were also examined for the presence of a tachycardia, raised jugular venous pressure, displaced apex beat, added heart sounds, cardiac murmurs, lung crepitations and peripheral oedema. HF clinical status was ascertained according to clinical scores based on the NHYA classification of functional status²⁶⁷ and Framingham criteria for the clinical diagnosis of HF.⁸ Subjects with systolic or diastolic dysfunction without a history or clinical evidence of HF were considered to be in the preclinical phase of disease. Serum amino-terminal B-type natriuretic peptide (NT-proBNP) concentrations were measured with a fully automated electrochemiluminescence sandwich immunoassay (proBNP, Roche Diagnostics).

5.3.5 Quality of Life

The standardised Short-Form 36-item questionnaire was administered to assess general health status.

5.3.6 Statistical analysis

Continuous variables are presented as mean (SD). Categorical variables are displayed as percentages. Differences between groups were assessed by likelihood ratio tests (categorical variables) or Kruskal–Wallis tests and non-parametric tests for trend (continuous variables), as appropriate. We calculated the point estimate and 95% CI (by the exact binomial method) for DD (for any EF and for subjects with EF > 50%), stratified for five-year age groups and sex. Ordinal logistic regression was used to

assess the association between the ordinal variable, diastolic function grade and clinical or echocardiographic predictors in univariable and multivariable analyses, adjusted for age and sex and relevant covariates. Least squares linear regression was used to assess the relationship between general health status score and diastolic function grade, after adjustment for age, sex and significant covariates. All hypothesis testing was two sided, and significance was declared if $p < 0.05$. The assumptions for regression models were checked statistically.

5.4 RESULTS

5.4.1 Study participants

Seventy-five per cent (1388 of 1846) of the eligible subjects agreed to participate in the survey. The only groups with participation rates $< 70\%$ were women aged 75–79 years (68%) and > 80 years (49%). Consequently, compared with the source population, the sample population had a higher proportion of men (50.5% v 47.2%, $p < 0.012$) and were younger (68.9 years v 69.6 years, $p = 0.0005$). About 92% participants (1275 of 1388; mean age 69.4; 50% men) completed all the echocardiographic investigations necessary for assessment of LV function.

For 32 subjects, diastolic function grade could not be determined (atrial fibrillation with deceleration time of mitral E wave > 140 ms; mitral stenosis; mitral E:A fusion; and only a single criterion suggestive of moderate to severe DD). The prevalence of any DD was 34.7% (95% CI 32.1% to 37.4%) and that of moderate to severe DD was 7.3% (95% CI 5.9% to 8.9%). Table 5-2 presents the prevalence of DD stratified by age group, sex and EF status.

Table 5-2 Prevalence of diastolic dysfunction in the cohort (n = 1275) stratified by age group, sex and left ventricular ejection fraction status

	Age groups (years)					
	60–64	65–69	70–74	75–79	80–86	All
Diastolic dysfunction, any ejection fraction						
Mild						
Men	30 (15.3%)	39 (23.8%)	36 (31.0%)	29 (32.2%)	36 (51.4%)	170 (26.7%)
Women	31 (16.1%)	37 (24.8%)	45 (30.8%)	43 (41.7%)	23 (47.9%)	179 (28.0%)
All	61 (15.7%)	76 (24.3%)	81 (30.9%)	72 (37.3%)	59 (50.0%)	349 (27.4%)
Moderate or severe						
Men	10 (5.1%)	13 (7.9%)	8 (6.9%)	8 (8.9%)	8 (11.4%)	47 (7.4%)
Women	4 (2.1%)	6 (4.0%)	13 (8.9%)	14 (13.6%)	9 (18.8%)	46 (7.2%)
All	14 (3.6%)	19 (6.1%)	21 (8.0%)	22 (11.4%)	17 (14.4%)	93 (7.3%)
Diastolic dysfunction with normal ejection fraction						
Mild						
Men	28 (14.3%)	33 (20.1%)	29 (25.0%)	21 (23.3%)	23 (32.9%)	134 (21.1%)
Women	31 (16.1%)	35 (23.5%)	43 (29.5%)	37 (35.9%)	19 (39.6%)	165 (25.8%)
All	59 (15.2%)	68 (21.7%)	72 (27.5%)	58 (30.1%)	42 (35.6%)	299 (23.5%)
Moderate or severe						
Men	6 (3.1%)	9 (5.5%)	6 (5.2%)	4 (4.4%)	7 (10.0%)	32 (5.0%)
Women	2 (1.0%)	6 (4.0%)	12 (8.2%)	14 (13.6%)	6 (12.5%)	40 (6.3%)
All	8 (2.1%)	15 (4.8%)	18 (6.9%)	18 (9.3%)	13 (11.0%)	72 (5.6%)

Table 5-3 outlines the univariate associations between clinical characteristics and diastolic function. Higher age was associated with any DD ($p < 0.0001$) and moderate to severe DD (3.6% in subjects aged 60–64 years ν 14.4% in subjects aged > 80 years, $p_{\text{trend}} < 0.001$), but rates of any DD ($p = 0.68$) or moderate to severe DD did not differ significantly between men and women (7.4% ν 7.2%, respectively, $p = 0.90$).

Table 5-3 Clinical characteristics of participants according to left ventricular diastolic function status

	Normal (n=801)	Diastolic Dysfunction, any EF		p-value
		Mild (n=349)	Moderate/Severe (n=93)	
Age (yrs)	68 \pm 6	72 \pm 7	73 \pm 7	<0.0001
Women, n (%)	403 (50.3)	179 (51.3)	46 (50.0)	0.94
Systolic blood pressure (mmHg)	137 \pm 17	140 \pm 17	139 \pm 18	0.001
Hypertension, n (%)	337 (42.0)	191 (54.7)	58 (63.0)	<0.0001
Angina, n (%)	75 (9.4)	53 (15.2)	22 (23.9)	<0.0001
Myocardial Infarction, n (%)	37 (4.6)	33 (9.5)	20 (21.7)	<0.0001
Diabetes, n (%)	73 (9.1)	37 (10.6)	18 (19.6)	0.007
Obese, n (%)	223 (27.8)	98 (28.1)	39 (42.4)	0.01
Excessive alcohol intake, n (%)	30 (3.7)	18 (5.2)	6 (6.5)	0.32

After adjustment for age and sex, a history of hypertension ($p = 0.002$), diabetes ($p = 0.03$), angina ($p = 0.048$), myocardial infarction ($p < 0.0001$), overweight ($p = 0.01$) and obesity ($p < 0.0001$) were associated with DD (Table 5-4).

Table 5-4 Association between clinical and echocardiographic parameters and left ventricular diastolic dysfunction

	Adjusted OR (95% CI)*	p-value
Men	0.97 (0.76 to 1.23) †	0.78
Age group (referent: 60–69 years)		
70–79 years	2.5 (1.9 to 3.2) ‡	<0.0001
80–86 years	5.7 (3.9 to 8.4) ‡	<0.0001
Hypertension	1.5 (1.2 to 2.0)	0.002
Diabetes	1.4 (1.03 to 2.0)	0.029
Myocardial infarction	2.8 (1.8 to 4.4)	<0.0001
Coronary disease	1.8 (1.3 to 2.4)	<0.0001
Body mass index (referent: <25 kg/m ²)		
25–29.9 kg/m ²	1.5 (1.1 to 2.0)	0.01
≥30 kg/m ²	1.9 (1.3 to 2.6)	<0.0001
Ejection fraction ≤50%	5.4 (3.3 to 8.8)	<0.0001

**Adjusted for age and sex unless specified; †adjusted for age; ‡ adjusted for sex.*

Rates of DD increased with decreasing EF ($p=0.0001$). Indeed, there were no subjects with an $EF \leq 40\%$ with normal LV diastolic function.

5.4.2 Diastolic dysfunction with normal ejection fraction

The prevalence of moderate to severe DD with an EF > 50% and no regional LV wall motion abnormalities was 5.6% (95% CI 4.4% to 7.1%). Rates of DD-NEF increased with age ($p < 0.0001$) but did not differ between men and women ($p = 0.34$). Clinical predictors of DD-NEF were a history of HT ($p < 0.0001$), angina ($p = 0.04$), myocardial infarction ($p = 0.003$), and obesity ($p < 0.0001$). Figure 5-1 presents the impact of cardiovascular risk factors on age-specific rates of DD-NEF. Of subjects aged < 70 years and without a history of HT, ischaemic heart disease, diabetes or obesity, advanced DD-NEF was documented in only one person.

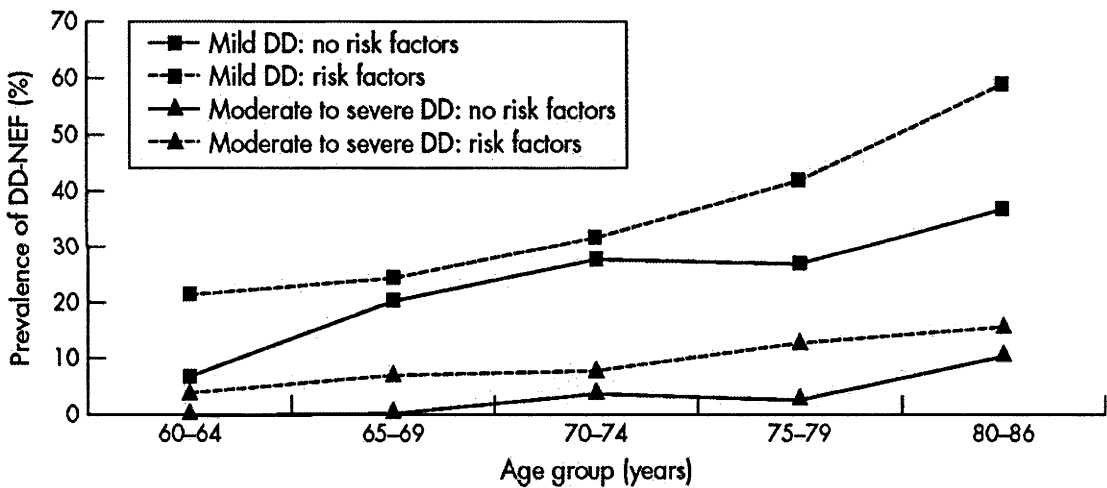


Figure 5-1 Impact of cardiovascular risk factors on age-specific rates of DD-NEF.

Risk factor status was dichotomised according to history of the risk factors; hypertension, ischaemic heart disease (angina or myocardial infarction), obesity, and diabetes.

Doppler evidence of moderate or severe DD-NEF was accompanied by echocardiographic and biochemical markers of impaired LV relaxation and increased LV filling pressure. Even after we controlled for age, sex and EF, worsening DD-NEF was associated with an increase in indexed LA volume ($p < 0.0001$) and NT-proBNP concentration ($p < 0.0001$). Indexed LA volume ($p = 0.61$) and NT-proBNP concentration ($p = 0.10$), however, did not differ significantly between subjects with normal and those with mild DD, even after stratification for age and sex.

In subjects with DD-NEF, there was evidence of LV remodelling and alterations in long axis systolic function (Table 5-5). LV mass index ($p < 0.0001$) and mitral annular systolic velocity increased with advancing DD, independent of age and gender. However, EF did not significantly decrease in subjects with DD-NEF ($p_{\text{trend}} = 0.11$).

Quality of life, as assessed by general health status (Table 5-5), progressively deteriorated with increasing severity of DD-NEF, independent of age, gender, overweight/obesity status, past history of HT, diabetes or ischaemic heart disease or EF ($p < 0.0001$).

Table 5-5 Echocardiographic and other characteristics of participants with normal ejection fraction by diastolic function status

		Diastolic dysfunction, normal EF†		
	Normal* (n = 755)	Mild (n = 299)	Moderate to severe (n = 72)	p-value
Age (years)	68 (6)	71 (7)	73 (6)	<0.0001
Women	394 (52.2%)	165 (55.2%)	38 (54.3%)	0.34
General health status score (/100)	69 (22)	63 (24)	54 (26)	<0.0001
EF(%)	68 (5)	67 (5)	66 (7)	0.11
Mitral annular systolic velocity (cm/s)	10.6 (3)	10.8 (3)	8.4 (2)	<0.0001
LVEDD index (cm/m ²)	2.67 (0.3)	2.68 (0.4)	2.70 (0.3)	0.31
LV mass index (g/m)	100 (24)	106 (31)	121 (33)	<0.0001
Left atrial volume index (ml/m ²)	22.4 (6.6)	23.4 (8.3)	37.5 (14)	<0.0001
Mitral annular diastolic velocity (cm/s)	10.1 (2)	8.6 (2)	8.5 (2.8)	<0.0001
Amino-terminal pro-BNP (pmol/l)	14 (13)	19 (31)	105 (164)	<0.0001

**Ejection fraction (EF) >50%, no regional wall motion abnormalities and normal diastolic function; †EF >50% and no regional wall motion abnormalities.*

5.4.3 Relationship between DD-NEF and heart failure status

Of subjects with a previous diagnosis of HF, 47% (95% CI 35% to 59%) had an EF > 50% and no evidence of regional wall motion abnormalities. Of subjects with moderate to severe DD-NEF, 86% were in the preclinical stage of disease as assessed by strict Framingham criteria. Even when clinical status was judged by the NYHA classification, 36% of subjects with moderate to severe DD-NEF were asymptomatic. Thus, about one in 20 subjects in the sample population had preclinical advanced DD-NEF (4.9%, 95% CI 3.7% to 6.2%). In contrast, preclinical advanced systolic dysfunction (EF ≤ 40%) was rare (0.5%, 95% CI 0.2% to 1.0%).

Markers of progression from preclinical DD-NEF to overt HF were decreased EF (66% in preclinical advanced DD-NEF v 59% in clinical advanced DD-NEF, $p = 0.003$), increased NT-proBNP concentration (84 pmol/l v 248 pmol/l, $p = 0.03$) and trends towards increased LV end diastolic size (2.67 cm/m^2 v 2.83 cm/m^2 , $p = 0.13$) and indexed LA volume (36.3 ml/m^2 v 45.1 ml/m^2 , $p = 0.11$).

5.5 DISCUSSION

In this population-based sample of older adults, DD was common and increased in frequency with age. In contrast to the female preponderance documented in studies of HF with normal EF,²⁶⁵ we found that DD was equally common in men and women. Co-morbid cardiovascular conditions such as HT, ischaemic heart disease, diabetes, obesity and systolic dysfunction were predictors of DD, independent of age and sex. Advanced (moderate or severe) DD rarely equated to "diastolic" HF. Indeed, 76% of

patients with advanced DD did not have overt symptoms or a history of HF. We observed that advanced DD-EF was as common as systolic dysfunction ($EF \leq 50\%$) and more likely to be present in the preclinical phase of disease. Despite the frequent absence of symptoms, subjects with advanced DD-NEF had evidence of structural remodelling, including increased LA size and LV mass, and raised NT-proBNP concentrations compared with subjects with normal or mildly impaired diastolic function. Furthermore, DD-NEF was independently associated with a reduction in general health status.

Several factors enhance the validity of results from this study compared with previously published surveys. Our estimates of systolic and diastolic dysfunction are less likely to be affected by selection bias arising from a low participation rate²⁰ or misclassification error resulting from the failure to use comprehensive Doppler methods to distinguish subjects with normal diastolic function from those with moderate DD.⁵⁹ Nonetheless, the consistency in prevalence and clinical predictors of DD between our study and the only other study that employed detailed Doppler methods of estimating LV filling pressure⁵ provides reassurance as to the generalisability of our findings.

5.5.1 DD-NEF and HF status

This study extends previously published observations on the relationship between DD-NEF and HF status.²⁰ In addition to surveillance of medical records, the incorporation of a clinical examination to detect symptoms and signs of HF has provided a more robust classification of clinical status of subjects with DD-NEF. By

using an array of clinical scores that offer varying degrees of sensitivity and specificity, we have confirmed the existence of a preclinical phase of advanced DD that is detectable by comprehensive Doppler echocardiography. Indeed, the prevalence of preclinical advanced DD-NEF is 10-fold greater than that of advanced systolic dysfunction. There is scant evidence regarding the prognostic significance of preclinical DD. Despite their lack of symptoms, subjects with preclinical advanced DD-NEF have biochemical and morphological evidence supporting the presence of current and chronic rise of LV filling pressures as assessed by NT-proBNP concentration and LA size, respectively. Further, as LA size has been shown to be an independent risk marker for the development of atrial fibrillation,^{268, 269} stroke,²⁷⁰ incident HF²⁷¹ and cardiovascular death,²⁷² preclinical DD-NEF is likely to be a condition that portends a poor cardiovascular prognosis. Our conclusion is supported by longitudinal data from a study of Olmsted County residents, which has shown that people with advanced DD, most of whom were in a preclinical stage of disease, had a 10-fold higher risk of all cause death than subjects with normal diastolic function after adjustment for age, sex and EF.²⁰

5.5.2 “Isolated” LV diastolic dysfunction

Despite evidence from convenience samples that patients with HF^{118, 273, 274} or DD-NEF have a subtle decrease in LV long-axis systolic dysfunction,^{141, 274} subjects with DD with an EF > 50% have recently been classified as having isolated DD.²⁰ Our results suggest that this term may be an oversimplification. We have observed that, in subjects with an EF > 50% and no regional wall motion abnormalities, advancing DD

was associated with a decrease in long-axis systolic function and HF status was related to a reduction in radial systolic function, although EF remained within "normal" limits. Furthermore, there was a trend towards an increase in LV end diastolic size with advancing DD and in subjects with symptomatic DD-NEF. Thus, at least some subjects with advanced DD-NEF may have cardiac remodelling as a pathophysiological response to co-morbid cardiovascular conditions (HT, ischaemic heart disease or obesity), with increased LV filling pressure related to an increased ventricular capacitance rather than a shift in the end diastolic pressure–volume relationship caused by a pure decrease in LV compliance. Although recent studies have provided an insight into the mechanisms underlying such a response by showing that patients with advanced DD-NEF have load-dependent alterations in diastolic function caused by increased LV systolic and arterial stiffness,²⁷⁵ more work is required to confirm these findings.

5.5.3 Limitations

A low participation rate from women aged >80 years may have resulted in an underestimation of the true prevalence of LV dysfunction in the source population. Although echocardiography is widely accepted as a safe and convenient method for the diagnosis and follow up of patients with DD,¹²³ it is recognised that Doppler echocardiographic methods reflect integrative properties of diastolic function that lack specificity.²⁷⁶ In this study of survey participants, we could not justify the use of invasive methods for the assessment of active and passive diastolic LV properties. Most (97.6%) of our sample was white and our results may not be applicable to non-white populations. As our data are cross sectional, we were unable to determine

temporal relationships (and thus causal relationships) between clinical parameters, cardiac remodelling and diastolic function.

5.5.4 Implications

The burden of DD-NEF in the community will probably increase with the ageing population and escalating rates of obesity and diabetes in the community. Whether this burden can be reduced by screening efforts remains to be determined. Our observations suggest that, as preclinical advanced DD-NEF is relatively common and associated with cardiac markers that portend a poor cardiovascular prognosis, screening efforts may be warranted. Before community-based screening programs for LV (systolic and diastolic) dysfunction are adopted, however, more data are required detailing the natural history of the disease, the efficacy of treatment for preclinical LV dysfunction, the screening performance of biomarkers and ultimately the cost effectiveness of screening strategies. As DD-NEF is rare in subjects without co-morbid cardiovascular conditions, the efficiency of screening programs could be optimised by targeting high-risk groups, defined according to age (> 70 years) or risk factor status (HT, ischaemic heart disease, diabetes or obesity).

5.5.5 Conclusion

DD is common in the community and is often unaccompanied by overt symptoms and signs of HF. Despite the absence of symptoms, subjects with advanced DD-NEF

have accompanying structural abnormalities that reflect an increased risk for adverse cardiovascular outcomes and have a reduced quality of life.

Chapter 6: AMINO- TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE AS A MARKER OF LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC DYSFUNCTION IN THE COMMUNITY

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6.1 ABSTRACT

Background. There is limited information regarding the clinical utility of aminoterminal B-type natriuretic peptide (NT-proBNP) for the detection of left ventricular (LV) dysfunction in the community. We evaluated predictors of circulating NT-proBNP levels, and determined the utility of NT-BNP to detect systolic and diastolic LV dysfunction in older adults.

Methods. A population-based sample of 1229 older adults underwent echocardiographic assessment of cardiac structure and function and measurement of circulating NT-proBNP levels.

Results. Predictors of NT-proBNP included age, female gender, body mass index, and cardiorenal parameters (diastolic dysfunction [DD] severity; LV mass and LA volume; right ventricular overload; decreasing ejection fraction [EF] and creatinine clearance). The performance of NT-proBNP to detect any degree of LV dysfunction, including mild DD, was poor (AUC 0.56-0.66). In contrast, the performance of NT-proBNP for the detection of $EF \leq 40\%$ and moderate-severe DD was strong with $AUC > 0.90$ regardless of age and gender. The ability of NT-proBNP to detect $EF \leq 40\%$ and/or moderate-severe DD was optimised by using age/gender-specific limits (men 60-74, 20pmol/L; women 60-74, 30pmol/L; ≥ 75 years, 45pmol/L). Of “false positive” tests, 88% (126/143) were explained after considering cardiorenal determinants of NT-proBNP levels.

Conclusions. NT-proBNP is a suboptimal marker of mild LV dysfunction, but performs strongly as a marker of $EF \leq 40\%$ and/or moderate-severe DD in the community.

6.2 BACKGROUND

The natriuretic peptides are a structurally and functionally distinct group of peptides that play an important role in the regulation of cardiovascular and renal homeostasis. Recent studies have assessed the utility of natriuretic peptides in distinguishing between cardiac and non-cardiac dyspnea in the emergency department,^{167, 277} as a prognostic tool in patients with HF^{278, 279} and acute coronary syndromes,^{280, 281} and as a guide to medical therapy in patients with chronic HF.^{282, 283} However, in a recent review of the diagnostic utility of natriuretic peptides for the detection of left ventricular (LV) dysfunction and HF, it was concluded that the body of evidence is “still a work in progress”.²⁸⁴ In particular, there are several limitations with studies that have sought to establish the clinical utility of natriuretic peptides for the diagnosis of left ventricular dysfunction. Often such studies are done using convenient samples in which cardiac structure and function are poorly characterised. Furthermore, most studies have focused on the utility of natriuretic peptides for the detection of systolic ventricular dysfunction, ignoring prognostically significant DD.²⁰ Another important limitation of previous studies is their failure to evaluate the influence of the multiple determinants of circulating natriuretic peptides on the performance of the tests. Such information on the clinical validation of natriuretic peptide assays is a prerequisite for their optimal use as diagnostic tools in the community.²⁸⁵

The objectives of this study were to determine the clinical and echocardiographic determinants of circulating aminoterminal B-type natriuretic peptide (NT-proBNP) levels (proBNP®; Roche Diagnostics) in a population-based sample of older adults,

establish reference ranges in subjects that have been rigorously assessed to be free of cardiovascular disease, and to evaluate the ability of NT-proBNP to detect subjects with LV systolic and diastolic dysfunction in the community. We hypothesised that a large proportion of apparent “false positives” could be explained after considering determinants of NT-proBNP levels.

6.3 METHODS

6.3.1 Subjects

Using simple random sampling from a population register (Federal electoral roll), 2000 Canberra residents, aged 60-85, were selected to constitute our study population. Subjects were invited to participate by letter. Subjects provided written and informed consent, and 1229 participants (mean age 69.4; 50.1% women) completed all investigations relevant to this study between February 2002 and June 2003.

6.3.2 Clinical assessment

Risk factors for HF were documented using a self-administered questionnaire. Body mass index was calculated as the weight divided by the squared height. Volume status was assessed clinically according to the jugular venous pressure, the presence of peripheral oedema and cardiorespiratory auscultation. Functional status was assessed using the NYHA classification.²⁸⁶ Creatinine clearance (CrCl) was calculated by applying relevant data to the Cockcroft-Gault formula.²⁸⁷

6.3.3 Lifestyle factors

A validated, interviewer-administered physical activity questionnaire²⁸⁸ was used to assess time spent on physical activity during the preceding week, adjusting for the intensity of the activity. Data was collected on smoking status (non-smoker or current smoker), alcohol consumption (none, $\leq 20\text{g/day}$ and $> 20\text{g/day}$) and daily consumption of caffeine-containing tea and coffee.

6.3.4 Cardiac structure and function

Transthoracic echocardiography was performed using the Acuson 128 XP/10 according to a standardised protocol. Studies were recorded on tape and reviewed off-line by a cardiologist who was blinded to the participant's clinical data. LV mass was estimated by the area-length method²⁸⁹ and indexed for height. EF was quantified by the biplane Simpson method using the 2-dimensional images from the apical 4- and 2-chamber views. Abnormal LV systolic function was categorised according to EF and the presence of regional wall motion abnormalities (regional wall motional abnormalities with $\text{EF} > 50\%$; $\text{EF} 41\text{-}50\%$; $\text{EF} \leq 40\%$). DD was graded into 3 categories using Doppler evaluation of the mitral and pulmonary venous inflow and tissue Doppler imaging of the lateral mitral annulus motion (Table 6-1).

Table 6-1 Doppler assessment of left ventricular diastolic function

	Mitral inflow	Pulmonary venous inflow	TDI MAM
Normal	$0.75 < E/A < 1.5$ $DT > 160\text{ms}$	$S > D$ $MV\text{ Adur} > PV\text{ Adur}$	$E/e' < 10$
Mild LV diastolic dysfunction	$E/A < 0.75$ $DT > 240\text{ms}$	$S > D$ $MV\text{ Adur} > PV\text{ Adur}$	$E/e' < 10$
Moderate LV diastolic dysfunction	$0.75 < E/A < 1.5$ $DT > 160\text{ms}$	$S < D$ $MV\text{ Adur} + 30\text{ms} < PV\text{ Adur}$	$E/e' \geq 10$
Severe LV diastolic dysfunction	> 1.5 $DT < 160\text{ms}$	$S < D$ $MV\text{ Adur} + 30\text{ms} < PV\text{ Adur}$	$E/e' \geq 10$

At least 2 Doppler criteria consistent with moderate-severe DD were required to distinguish from normal diastolic function. E, peak early mitral inflow filling velocity; A, peak mitral filling velocity at atrial contraction; DT, deceleration time of mitral E wave; MV Adur, duration of mitral A wave; S, peak velocity of pulmonary venous forward flow during systole; D, peak velocity of pulmonary venous forward flow during diastole; PV Adur, duration of pulmonary venous reversal wave at atrial contraction; e', peak velocity of lateral mitral annulus motion during early diastole. TDI MAM = Tissue Doppler imaging of mitral annular motion

Subjects with indeterminate LV diastolic function and $EF > 40\%$ were excluded for evaluation of optimal discriminatory NT-proBNP levels. Maximum LA volume was quantified using the area-length method and indexed for body surface area (LAVI). Aortic and mitral valve function were quantified using Doppler methods. The presence of right ventricular (RV) volume or pressure overload was determined using

2-dimensional images of the right ventricle from the parasternal long and apical 4-chamber views and the RV systolic pressure estimated by Doppler assessment of tricuspid regurgitant jet.

6.3.5 NT-proBNP levels

Venous blood was collected in serum tubes, centrifuged and stored at -70°C until analysis. NT-proBNP levels were measured using a commercially available and fully automated electrochemiluminescence sandwich immunoassay on an Elecsys 1010 (proBNP®, Roche Diagnostics). This immunoassay has a within run coefficient of variability (CV) of 0.7-1.6% and a between run CV of 5.3-6.7%.²⁵³

6.3.6 Statistical analysis

NT-proBNP levels were positively skewed and natural log-transformation was required to satisfy statistical modeling assumptions for regression analyses. For the entire cohort, echocardiographic and clinical variables were assessed for their univariate association with NT-proBNP using Spearman rho correlation. Variables with statistically significant associations with log NT-proBNP in the univariate analysis were included in the stepwise multivariable linear least-squares regression analysis, starting with a full model (STATA version 7.0, Texas, USA).

The reference subgroup considered for the derivation of reference ranges of NT-proBNP excluded subjects with atrial fibrillation, myocardial infarction, HT, diabetes, renal impairment ($\text{creatinine} \geq 150 \mu\text{mol/l}$), echocardiographic evidence of

abnormal cardiac structure/function (dilated cardiac chambers including LAVI>28mL/m², LV hypertrophy, abnormal LV systolic function, any DD, more than mild mitral or aortic valve disease and elevated RV systolic pressure), past or current clinical HF. Subjects on antihypertensive or diuretic medication were also excluded from the reference group. Analytical methods used on the entire cohort were employed to determine associations of NT-proBNP in the reference subgroup, and the result of the multivariable regression analysis was used to determine which parameters required partitioning in order to more accurately reflect NT-proBNP reference levels. From the least-squares regression model for log(NT-proBNP) with age and gender as predictor variables, 5th to 95th percentiles were estimated and back-transformed to the natural scale to derive gender-specific reference NT-proBNP ranges.

The ability of NT-proBNP to detect varying degrees of LV systolic and/or diastolic dysfunction in the entire cohort (n=1207) was assessed using receiver operating characteristic (ROC) analysis. The overall performance for the test over its entire range was quantified using the area under the ROC curve (AUC) curves within age- and gender-specific strata and compared using the method of DeLong.²⁹⁰ The diagnostic performance of NT-proBNP to detect LV dysfunction was evaluated using cutoff points based on:

- i) age and gender-specific optimal discriminatory levels, identified as the NT-proBNP level that corresponded to the point on the ROC curve at the minimum distance to the 100% sensitivity/100% specificity point
- ii) age- and gender-specific 95th percentiles from the reference subgroup

- iii) recommended decision threshold levels based on clinical data from Roche Diagnostics²⁹¹

6.4 RESULTS

6.4.1 Distribution of NT-proBNP levels

NT-proBNP levels are presented in Figure 6-1, stratified according to gender and LV function. There was a large overlap in NT-proBNP levels between groups with normal LV function and mild “isolated” DD (with EF>50%). However, NT-proBNP levels increased progressively with deteriorating LV function thereafter (all $p<0.0001$). In subjects with advanced isolated DD, NT-proBNP levels were higher than those with EF of 41-50% ($p=0.002$), but lower than subjects with EF \leq 40% ($p=0.001$).

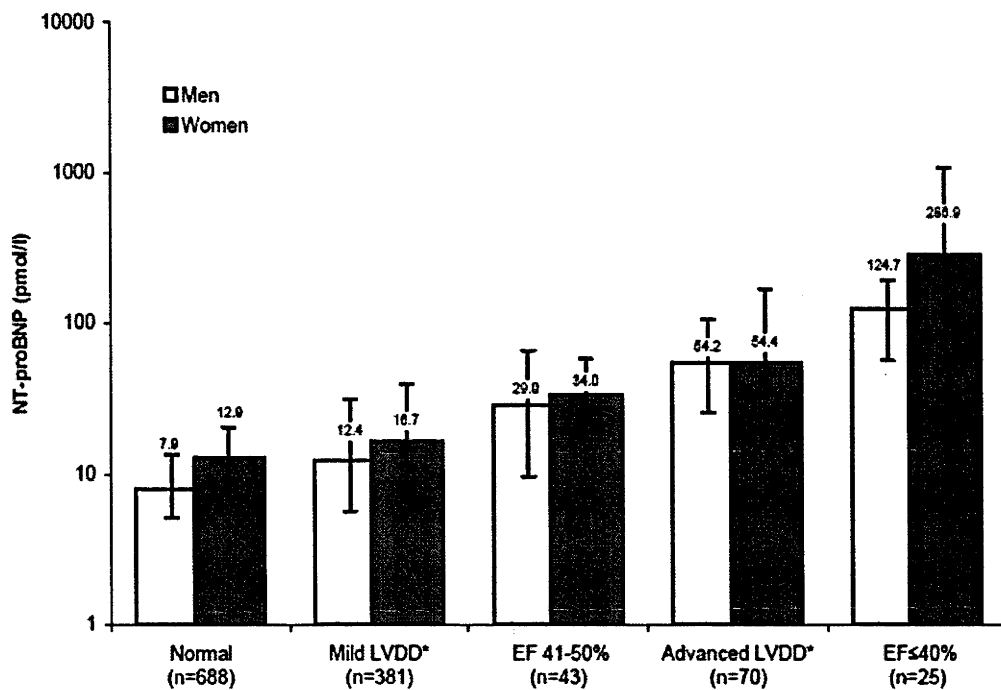


Figure 6-1 Median (bars) and interquartile range (error bars) for NT-proBNP levels according to gender and LV function.

*NT-proBNP levels are presented in the logarithmic scale. *Mild DD and Advanced DD refer to diastolic dysfunction with EF>50%.*

6.4.2 Associations with NT-proBNP in the entire cohort (n=1207)

In univariate analysis, age ($\rho=0.46$), CrCl ($\rho=-0.41$) and LAVI ($\rho=0.41$) were most strongly correlated with NT-proBNP levels. All variables included in the multivariable model were associated ($p<0.01$) with NT-proBNP in univariate analysis. Associations between NT-proBNP and clinical and echocardiographic variables in the entire cohort in the multivariable analysis are reported in Table 6-2.

Table 6-2 Multivariable associations with NT-proBNP levels in the entire cohort

Predictor (increment)	β^*	95%CI	p-value
Age (per 1 year)	1.03	1.02, 1.04	<0.0001
Women	1.39	1.27, 1.51	<0.0001
Volume overload	1.16	1.03, 1.31	0.017
Functional Class			
NYHA Class II	1.13	1.03, 1.23	0.007
NYHA Class III	1.48	1.18, 1.86	0.001
NYHA Class IV	4.32	1.16, 16.1	0.03
LV systolic function			
RWMA, EF>50%	1.40	1.15, 1.71	0.001
EF 41-50%	1.82	1.48, 2.24	<0.0001
EF 31-40%	2.38	1.65, 3.42	<0.0001
EF≤30%	2.98	1.86, 4.76	<0.0001
LV diastolic function			
Mild DD	0.94	0.87, 1.03	0.176
Moderate DD	2.24	1.85, 2.70	<0.0001
Severe DD	4.87	2.62, 9.04	<0.0001
LV mass index (per 5 g/m)	1.02	1.01, 1.03	<0.0001
Left atrial volume index (per ml/m ²)	1.01	1.01, 1.02	<0.0001
RV volume/pressure overload	1.28	1.00, 1.67	0.049
Creatinine Clearance (per mL/min)	0.99	0.99, 0.99	<0.0001
Body Mass Index (per kg/m ²)	0.98	0.97, 0.99	0.004
Pulse Pressure (per 5mmHg)	1.03	1.01, 1.04	0.001
Atrial Fibrillation	2.69	2.02, 3.59	<0.0001

** β -coefficient is back-transformed to natural scale. Adjusted R^2 for model=0.60.*

NYHA = New York Heart Association; RV = right ventricular; RWMA = regional wall motion abnormality.

6.4.3 Associations with NT-proBNP in the reference subgroup (n=201)

In univariate analysis, increasing age ($\rho=0.34$, $p<0.0001$) and LAVI ($\rho=0.15$, $p=0.03$); female gender ($p<0.0001$); decreasing CrCl ($\rho=-0.31$ $p<0.0001$); and coffee consumption ($p=0.038$) were associated with increased NT-proBNP levels. There was no association between NT-proBNP and heart rate ($\rho=-0.07$, $p=0.33$), physical activity levels over the preceding week ($\rho=-0.03$, $p=0.65$), tobacco smoking ($p=0.53$), or tea ($p=0.79$) consumption. NT-proBNP levels were not higher in healthy women on hormone replacement therapy ($p=0.64$), even after adjusting for age ($p=0.51$). Age, gender and LAVI were the only independent predictors of NT-proBNP levels in the reference subgroup. The addition of LAVI marginally improved the multivariable model for the prediction of NT-proBNP levels (R^2 0.24 to 0.25) and did not significantly alter the β -coefficients for age and gender. Thus for simplicity, results of the multivariable analysis with age and gender as the only predictor variables were used to construct nomograms for NT-proBNP reference levels (Figure 6-2).

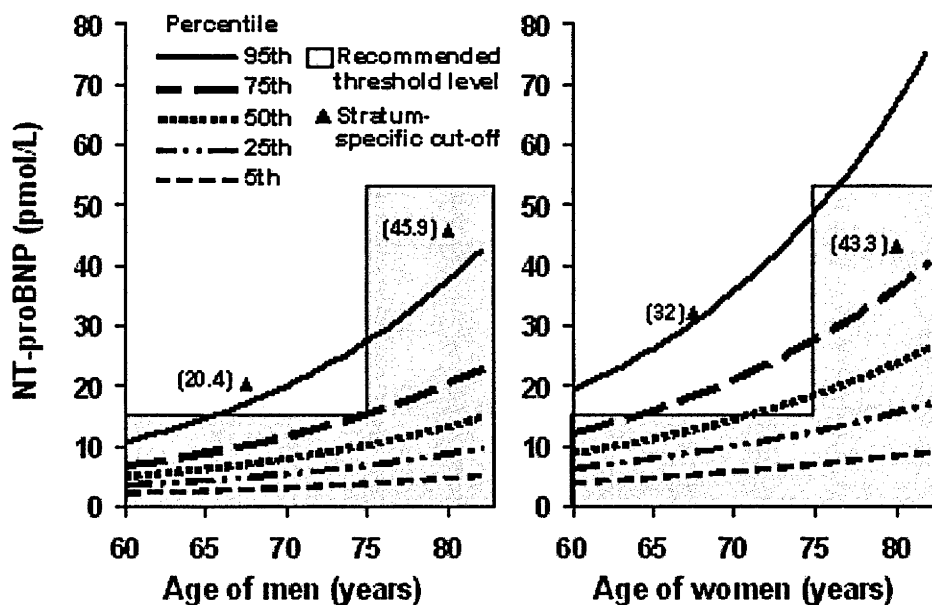


Figure 6-2 NT-proBNP (Roche Diagnostics) reference ranges.

Reference limits are illustrated as 5th, 25th, 50th, 75th, and 95th percentile levels. Cutoff NT-proBNP levels based on 95th percentiles, current recommended threshold levels and age/gender-specific optimal discriminatory points are compared.

6.4.4 NT-proBNP utility to detect LV dysfunction in entire cohort

The results of the ROC analyses for the detection of varying degrees of LV systolic and diastolic dysfunction are displayed in Figure 6-3.

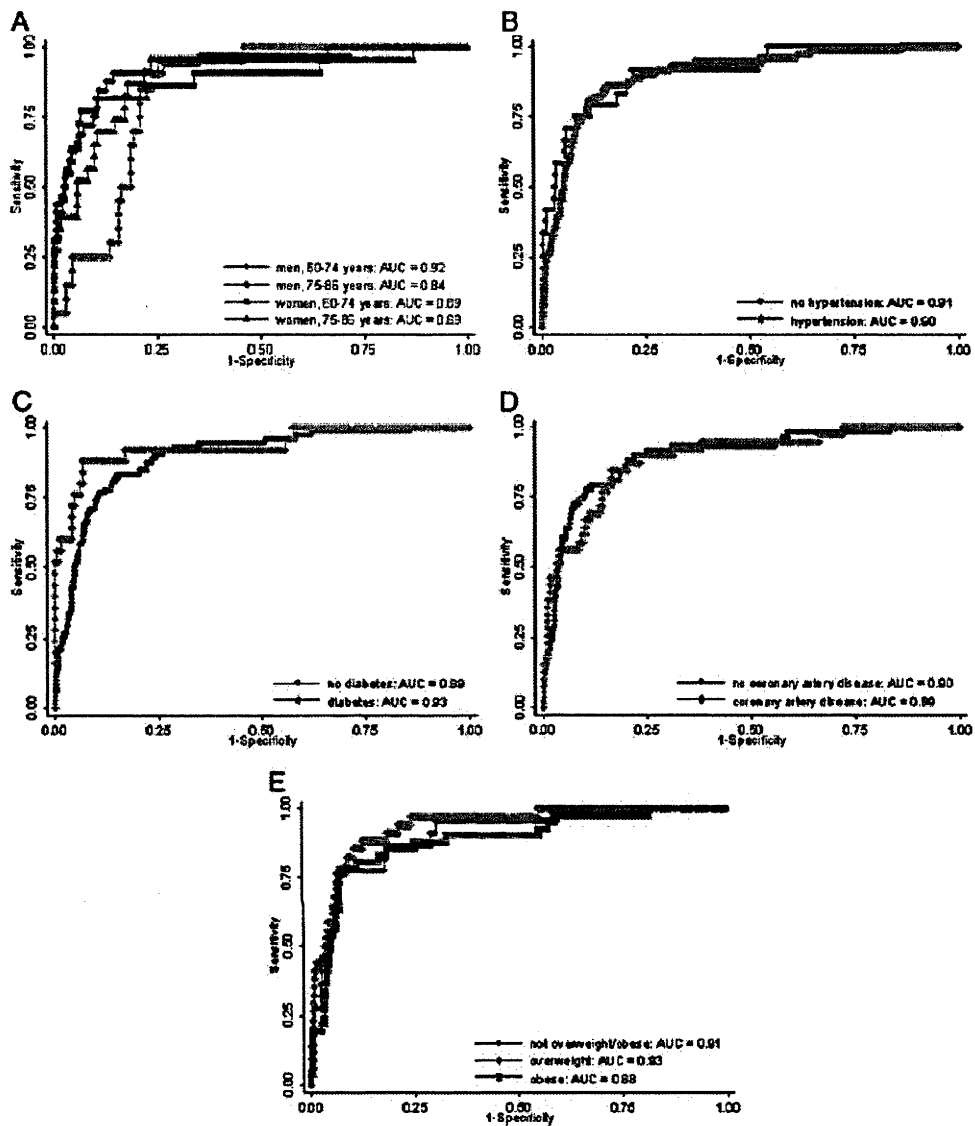


Figure 6-3 Overall performance of NT-proBNP for the detection of EF≤40% and/or moderate-severe DD, according to (A) age and sex ($P = 0.26$); history of (B) hypertension ($P = 0.83$); (C) diabetes ($P = 0.31$); (D) coronary artery disease ($P = 0.90$); or (E) body mass category ($P = 0.35$).

Age and gender did not impact on the overall performance of NT-proBNP to detect any degree of LV dysfunction ($p=0.19$); $EF \leq 50\%$ and/or advanced DD ($p=0.43$); or advanced LV dysfunction ($p=0.78$). The performance of NT-proBNP to detect any degree of LV dysfunction, including mild DD, was poor (AUC 0.56-0.66). In contrast, the performance of NT-proBNP for the detection of $EF \leq 40\%$ and moderate-severe DD was strong with AUC levels consistently above 0.90 regardless of age and gender. Further analysis of NT-proBNP performance has been limited to the detection of $EF \leq 40\%$ and moderate-severe DD, as this approach is more likely to represent the optimal use of NT-proBNP for the detection of LV dysfunction in the community.

Age and gender had a greater impact on 95th percentile reference limits than on optimal discriminatory NT-proBNP levels for the detection of $EF \leq 40\%$ and moderate-severe DD (Figure 6-3). The disparity between optimal discriminatory and reference limits was most evident for women aged ≥ 75 years. Consequently, in this subgroup, identification of LV dysfunction with 95th percentile reference limits resulted in an almost 3-fold increase in missed advanced LV dysfunction cases (Table 6-3).

Compared to optimal discriminatory levels, recommended decision threshold levels based on data from Roche Diagnostics were lower in subjects aged 60-74 years, particularly for women; and much higher in subjects aged ≥ 75 years. Consequently, application of currently recommended cutoffs resulted in an increased false positive rate in subjects aged 60-74 in whom disease prevalence was low, and an increased false negative rate for those aged ≥ 75 years in whom disease prevalence was higher.

CUTOFF STRATEGY	NT-PROBNP				MISSED		
	LEVEL		SENS	SPEC	DISEASE		
	pmol/L	pg/mL	(%)	(%)	LR+	LR-	(%)
Men 60-74 (Prevalence = 7.2% ; AUC=0.93, 95% CI 0.88-0.98)							
Stratum-specific ODP	20.4	173	88	89	7.8	0.14	12
95th Percentile	17.5	148	91	86	6.6	0.11	9
Recommended threshold	14.8	125	91	84	5.6	0.11	9
Men 75-86 (Prevalence = 14.2% ; AUC=0.90, 95% CI 0.84-0.95)							
Stratum-specific ODP	45.9	388	95	80	4.8	0.06	5
95th Percentile	37.5	317	95	76	4.0	0.06	5
Recommended threshold	53.2	450	86	85	5.5	0.17	14
Women 60-74 (Prevalence = 4.9% ; AUC=0.90, 95% CI 0.82-0.98)							
Stratum-specific ODP	32.0	270	83	91	9.6	0.19	17
95th Percentile	32.0	270	83	91	9.6	0.19	17
Recommended threshold	14.8	125	91	64	2.5	0.14	9
Women 75-86 (Prevalence = 16.4% ; AUC=0.91, 95% CI 0.83-0.98)							
Stratum-specific ODP	43.3	366	88	85	5.7	0.15	12
95th Percentile	66.6	563	67	92	7.9	0.35	33
Recommended threshold	53.2	450	75	89	5.9	0.29	25

AUC = area under receiver operating characteristic curve; LR+ =positive likelihood ratio; LR- =negative likelihood ratio; Missed disease = proportion of subjects with LV dysfunction who would have been missed with NT-proBNP test; ODP = optimal discriminatory point based on receiver operating characteristic curve analysis; Sens =sensitivity; Spec =specificity; Recommended threshold²⁹¹

Table 6-3 Performance of NT-proBNP in detecting EF ≤40% and/or moderate-severe DD

Using NT-proBNP cutoffs of 20pmol/L for men aged 60-74, 30pmol/L for women aged 60-74 and 40pmol/L for subjects aged ≥ 75 ; one subject with an LVEF $\leq 40\%$ (male, aged 67, EF=40%) and 10 subjects with moderate-severe DD (60% female, mean age 72 years) were missed with NT-proBNP testing. Of the 143 subjects with false positive tests, 70 subjects had milder degrees of LV dysfunction (20 with EF = 41-50%, 21 with LV regional wall motion abnormalities and EF $>50\%$; and 29 with impaired relaxation and evidence of increased LV filling pressure [as defined by Doppler-echo or an otherwise unexplained LAVI $>28\text{mL/m}^2$]); 21 with increased LV mass ($>132\text{g/m}$ for women and $>157\text{g/m}$ for men); 16 with LAVI $>28\text{mL/m}^2$ and no evidence of DD or mitral valve disease; 4 with dilated RV; and 15 with CrCl $<60\text{ml/min}$. Only 17 individuals did not have an identifiable cardiorenal cause for an elevated NT-proBNP level.

6.5 DISCUSSION

In this large population-based cohort of older adults, some of the complexities of using NT-proBNP as a tool for the detection of LV dysfunction have been identified and explored.

6.5.1 Determinants of NT-proBNP

An understanding of the determinants of NT-proBNP in the community is a prerequisite for its optimal use as a diagnostic tool for LV dysfunction. Results of our multivariable analysis could serve as a guide to determine the extent to which each factor influences NT-proBNP and identify potential sources of elevated NT-proBNP

levels other than parameters of LV function, which may be the cause of apparent “false positive” tests.

Our observations provide a valuable insight into the relationship between natriuretic peptides and mild isolated diastolic function, a topic of recent dispute. Lubien et al¹⁷⁶ assessed the relationship between BNP levels and diastolic function in clinic-based patients with preserved systolic function. These investigators observed that BNP levels increased with progressive stages of DD and found that patients with mild DD had significantly higher BNP levels than those with normal diastolic function.¹⁷⁶ Indeed, they found that the performance of BNP for the detection of mild isolated DD was good (AUC 0.87). However, since then, several studies with differing study populations have provided conflicting results.²⁹²⁻²⁹⁴ We have confirmed that NT-proBNP levels were increased in subjects with advanced isolated DD, in whom LV filling pressures were raised. In a proportion of such cases, preload-dependent mitral inflow Doppler patterns were only mildly impaired. Such subjects are more likely to be symptomatic and to constitute cases of “mild” isolated DD in studies with samples referred to a clinic for LV assessment. However, in this population-based sample, we have shown that NT-proBNP was a poor marker of mild isolated DD.

6.5.2 Reference limits

Prior efforts to define NT-proBNP reference limits have been on clinic-based^{294, 295} or convenience samples²⁹¹. For instance, reference ranges cited by the manufacturer of the NT-proBNP assay used in this study were derived from a population that was

incompletely characterised by an assessment of cardiac function and structure and included subjects with diabetes, HT, pulmonary disease and renal insufficiency.²⁹¹ As expected, reference limits from such a heterogeneous population were higher than those derived in our population-based sample.

In this study, we have extended efforts by previous investigators to restrict the reference subgroup to subjects free of any identifiable cardiovascular disease. Comprehensive Doppler-echo methods were employed to exclude subjects with any DD from the reference subgroup. In addition, subjects with a dilated left atrium or significant renal dysfunction were excluded for the derivation of reference limits since these conditions have been recognised as subclinical markers of increased cardiovascular risk^{20, 296} and were independently associated with increasing levels of NT-proBNP in our cohort. Despite our efforts to rigorously define the reference subgroup, the association between age, gender and NT-proBNP levels was reconfirmed in this study. Accordingly, we have presented reference limits that are stratified according to age and gender. Data from longitudinal studies are required to determine if the increase in NT-proBNP levels with advancing age is related to occult pathophysiological rather than physiological influences, in which case age-specific reference limits may be unwarranted.

A novel and important aspect of this study was the evaluation of impact of lifestyle factors on the relationship between age, gender and NT-proBNP levels. Experimental animal studies have demonstrated that chronic moderate ethanol exposure results in a lowering of circulating BNP levels²⁹⁷ that may be related to an inhibition of natriuretic peptide gene expression.²⁹⁸ In our study, lifestyle factors did not alter the

impact of age or gender on NT-proBNP levels. Interestingly, despite excluding subjects with any DD, more than mild valvular heart disease and LA enlargement ($\geq 28\text{mL/m}^2$) from the reference subgroup, there was an independent positive association between LAVI and NT-proBNP levels. Since LA size is a marker of chronic diastolic burden,¹⁵⁵ this finding may reflect increases in NT-proBNP levels associated with a chronic exposure to DD that is undetectable by Doppler-echo assessment of resting instantaneous diastolic function grade.

6.5.3 NT-proBNP detection of LV dysfunction in the community

This is the first study to assess the value of NT-proBNP for the detection of LV dysfunction, including isolated DD as evaluated using comprehensive Doppler echocardiography, in a population-based sample. Previous studies have determined the performance of the assay to detect either systolic²⁹⁹⁻³⁰² or isolated DD²⁹⁴ in clinic-based populations.³⁰³ The evaluation of the performance of NT-proBNP to detect both systolic and predominantly diastolic LV dysfunction is important for a number of reasons. In recent years, it has been recognised that almost half of HF cases have an EF $>50\%$,⁵⁴ and that DD in the community confers an adverse prognosis.²⁰ Consequently, a contemporary assessment of LV function should routinely incorporate an assessment of both systolic and diastolic function. Furthermore, given the large overlap in NT-proBNP levels between subjects with systolic dysfunction and predominantly DD, the specificity of NT-proBNP will appear to be reduced if its diagnostic role is limited to the detection of those with systolic dysfunction, due to “false negative” results in subjects with predominantly DD. Indeed, we have

confirmed that a large proportion of the “false positive” tests occurred in subjects with elevated NT-proBNP levels related to prognostically significant cardiorenal diseases. Since the impact of age and gender on reference limits was greater than their effect on optimal discriminatory levels, we would advise against a common practice of using reference limits as thresholds for the detection of LV dysfunction in the community. Such a strategy is likely to result in reduced NT-proBNP performance as a “rule out” test, particularly in older women.

Our results should not be extrapolated to patients presenting acutely with dyspnea for investigation. Since natriuretic peptide levels are also raised by non-cardiac causes of acute dyspnea, NT-proBNP cutoff levels have been set higher to optimise the diagnosis of acute HF in the emergency department.²⁷⁷ Moreover, the overall performance of the test is also likely to vary depending on the setting in which it is employed, although a recent study has shown that even in the emergency department, the performance of NT-proBNP for the diagnosis of acute HF was very good (AUC 0.94).²⁷⁷

6.5.4 Limitations

Echocardiographic methods are imperfect “gold” standards for the classification of systolic and diastolic function. However, these methods are currently accepted as the reference standard for the assessment of LV function in clinical practice, and we could not justify the evaluation of diastolic function in survey participants with

invasive tests. While our sample of older adults represents a suitable population for which natriuretic peptides would have potential use in the diagnosis or screening of HF, study findings may not be valid in younger subjects. As the vast majority of the sample was Caucasian, our results may not be applicable to non-Caucasian populations.

6.5.5 Conclusions

NT-proBNP is a suboptimal marker of mild LV dysfunction but performs strongly as a marker of $EF \leq 40\%$ and/or moderate-severe DD in the community.

Chapter 7: PULSE PRESSURE AND PULSE WAVE VELOCITY FOR THE DETECTION OF PRECLINICAL LEFT VENTRICULAR DYSFUNCTION IN THE COMMUNITY

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7.1 ABSTRACT

Objective: An age-dependent relationship between aortic and left ventricular (LV) stiffening has been observed in community-based adults. Our aim was to compare the performances of wave reflection-dependent (pulse pressure) and independent [carotid-femoral pulse wave velocity (PWV)] indexes of aortic stiffness to detect preclinical LV diastolic dysfunction.

Methods. In this case-control study, a stratified subsample of participants of a population-based echocardiographic survey with LV ejection fraction higher than 45% and without overt HF was randomly selected to undergo assessment of brachial BP, LV diastolic function by Doppler echocardiography, and estimation of central aortic pressures and PWV by applanation tonometry.

Results. Of the 233 subjects (mean age 73 ± 6 years, 54% men), 84 had normal diastolic function, 99 had mild diastolic dysfunction, and 50 had moderate or severe diastolic dysfunction. Brachial pulse pressure, central pulse pressure, and PWV progressively increased according to the severity of diastolic dysfunction, independent of age and sex. The overall performance of PWV was superior to brachial pulse pressure [area under receiver operating characteristic curve (AUC): 0.70 versus 0.59, respectively; $P = 0.005$] and central pulse pressure (AUC: 0.70 versus 0.56, respectively; $P = 0.001$) for the detection of any diastolic dysfunction.

Conclusion. PWV appeared to be superior to central and brachial pulse pressure for the detection of diastolic dysfunction in older adults with 'preserved' LV ejection fraction.

7.2 BACKGROUND

Recently, the prognostic value of two integrative markers of cardiovascular disease has been demonstrated in the general population. First, noninvasive indices of aortic stiffness such as pulse pressure and carotid-femoral pulse wave velocity (PWV) have been shown to predict cardiovascular outcomes in the community, independent of traditional risk factors.^{206, 207} Second, left ventricular (LV) diastolic dysfunction has been shown to be increasingly prevalent with advancing age and, although most frequently found in the preclinical phase of disease, is a predictor of all-cause mortality.²⁰

Although the mechanisms underlying the prognostic value of aortic stiffness and DD have not been fully determined, a common causal path way may be present whereby increased aortic stiffness promotes ventricular remodelling and the development of DD. Indeed, recent cross-sectional studies^{85, 86, 226, 275, 304-307} have observed age-related coupling of ventricular–vascular function and reported a positive association between aortic stiffness and DD. Whether measurement of aortic stiffness can be utilized to screen for DD in the community is not known.

In this population-based study, we evaluated the association between pulse pressure, PWV and diastolic function in subjects with ‘preserved’ EF. Furthermore, we compared the utility of PWV and pulse pressure to detect preclinical DD. We hypothesised that PWV would be superior to pulse pressure for screening DD, as the latter index of aortic stiffness, despite being easy to measure, is also influenced by other determinants of aortic wave reflection such as height and heart rate.

7.3 METHODS

7.3.1 Study population

In March 2002, 2000 Canberra residents of age 60–85 years were randomly selected from a general population list (Federal electoral roll) and invited to participate in an echocardiographic survey that was conducted in 2002–2003.³⁰⁸ The participation rate for the survey was 75%. In this nested case–control study, a subsample of participants with preserved systolic dysfunction ($EF > 45\%$) and without more than mild mitral or aortic valve disease was selected using stratified random sampling according to the diastolic function grade determined in the parent study, age (62–74 and ≥ 75 years) and sex. The participation rate for this study was 96% and subjects underwent assessment between February 2004 and June 2004. All participants provided informed consent.

7.3.2 Echocardiographic assessment of cardiac structure and function

Cardiac structure and function was assessed by one of two experienced sonographers using transthoracic echocardiography (Acuson Sequoia, Mountain View, California, USA) according to a standardised protocol. Measurements were made on-line and recorded digitally with participants' initials and study number as their only identification. A cardiologist, blinded to the participant's clinical data, interpreted the echocardiogram after review off-line. LV diastolic function was graded into four categories using Doppler evaluation of the mitral and pulmonary venous inflow and tissue Doppler imaging of the lateral mitral annulus motion as previously detailed [normal diastolic function; Grade 1 DD (impaired relaxation mitral inflow pattern);

Grade 2 DD (pseudonormal mitral inflow pattern); and Grade 3/4 DD (restrictive mitral inflow pattern)].³⁰⁹ Interoperator ($\kappa = 0.98$), intraobserver ($\kappa = 0.98$) and interobserver ($\kappa = 0.9$) reproducibility for diastolic function grading was very good. LV mass was quantified using the area-length method²⁴⁸ and indexed for body surface area. EF was quantified by the biplane disc summation method (Simpson's rule) using the two-dimensional echocardiography images from the apical four- and two-chamber views.²⁴⁸

7.3.3 Assessment of cardiovascular risk factors

A self-administered questionnaire was used to gather data on a history of CAD, HT, hyperlipidemia, diabetes and smoking status. Brachial artery systolic and diastolic BP was measured using a mercury sphygmomanometer after 10 min of rest in a seated position; three sets were averaged for each participant. Height and weight were measured without shoes and in light clothing. BMI was calculated for each participant as weight in kilograms divided by the square of height measured in metres.

7.3.4 Assessment of aortic pulse wave velocity

PWV was assessed noninvasively using the Sphygmocor system (AtCor Medical, Sydney, Australia) on the day of the echocardiography assessment and after an overnight fast. Electrocardiogram-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was measured as

the difference between the surface distances joining the suprasternal notch, the umbilicus and the femoral pulse and the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8–10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. PWV was calculated as the carotid-femoral path length divided by the carotid-femoral transit time.

7.3.5 Statistical analysis

Data are summarized as mean values \pm 1 SD for continuous variables or as frequency percents for categorical variables. Baseline characteristics of the sample were compared according to diastolic function status using Kruskal–Wallis tests for continuous variables and ordinal logistic regression for categorical variables.

The effects of age on pulse pressure, aortic stiffness, LV relative wall thickness, LV mass, LV filling pressure [as determined by the ratio of mitral inflow early diastolic velocity (E) and the early diastolic annular velocity (E_a); E/E_a] and LV relaxation (E_a) were assessed separately in men and women using Spearman [ρ] correlation. Age-adjusted associations between sex and log-transformed indices of arterial stiffness, LV mass, LV filling pressure and LV relaxation were evaluated using least-squares linear regression, and an interaction term with age and sex was assessed to determine whether the effect of age on the individual indices parameters varied according to sex.

Univariate associations between pulse pressure, PWV and clinical or echocardiographic parameters were assessed using Spearman [rho] correlation. Age/sex-adjusted associations between pulse pressure or PWV and selected echocardiographic parameters (dependent variable) were examined with least-squares linear regression. The association between diastolic function grade and clinical parameters, echocardiographic variables and pulse pressure or PWV was examined using multivariable ordinal logistic regression (STATA Version 8.0; STATA Corp., College Station, Texas, USA). The base model consisted of age, sex and pulse pressure or PWV and stepwise models were constructed by the addition of univariate clinical correlates ($p \leq 0.10$) of diastolic function grade, echocardiographic correlates of diastolic function grade and lastly BP parameters. First-order interactions between age, sex and echo-clinical predictors of diastolic function grade were also assessed in the model.

The utility of PWV to detect any level of DD or advanced (moderate or severe) DD was compared with that of pulse pressure using receiver-operating analyses. Areas under the receiver-operating characteristic curves (AUC) were compared using the method of DeLong et al.²⁹⁰ All hypothesis testing was two sided and statistical significance was declared if $p < 0.05$.

7.4 RESULTS

7.4.1 Clinical characteristics

Baseline characteristics of the 233 study participants (mean age 73 ± 6 years, 54% men) are outlined in Table 7-1, stratified by diastolic function status. Clinical correlates of DD included advancing age and a history of HT, diabetes mellitus and CAD.

Table 7-1 Baseline characteristics according to diastolic function grade*

	Normal DFG (n=84)	Grade 1 DD (n=99)	Grades 2-4 DD (n=50)	p-value
Age, y (SD)	71.2 (5.7)	73.8 (6.1)	76.2 (6.1)	<0.0001
Men, n (%)	45 (54)	58 (59)	23 (46)	0.58
Hypertension, n (%)	35 (42)	54 (55)	36 (72)	0.001
Diabetes, n (%)	4 (5)	11 (11)	7 (14)	0.06
Coronary artery disease, n (%)	9 (11)	12 (12)	12 (24)	0.05
Hyperlipidemia, n (%)	30 (36)	50 (51)	18 (36)	0.58
History of smoking, n (%)	48 (57)	62 (63)	20 (40)	0.14
Vasoactive medications, n (%)	29 (34)	59 (60)	35 (70)	<0.001
LV relative wall thickness	0.40 (0.07)	0.44 (0.09)	0.47 (0.17)	0.001
Indexed LV mass, g/m ² (SD)	89.6 (15.0)	105.8 (19.9)	117.3 (29.9)	<0.001
LV ejection fraction, % (SD)	65.8 (6.6)	63.6 (9.0)	66 (10)	0.71
Brachial systolic BP, mmHg (SD)	135 (17)	139 (19)	148 (20)	<0.0001
Central systolic BP, mmHg (SD)	128 (17)	130 (20)	140 (21)	<0.001
Brachial diastolic BP, mmHg (SD)	80 (7)	83 (10)	81 (10)	0.29
Central diastolic BP, mmHg (SD)	81 (7)	84 (10)	82 (10)	0.37
Brachial pulse pressure, mmHg (SD)	55 (16)	57 (15)	67 (17)	<0.001
Central pulse pressure, mmHg (SD)	47 (16)	47 (15)	58 (17)	<0.001
Mean arterial pressure, mmHg (SD)	99 (9)	103 (12)	104 (13)	0.02

**Preserved systolic function (LV ejection fraction >45%), no more than mild mitral or aortic valve disease. BP = blood pressure; DD = diastolic dysfunction*

A graded association existed between increasing severity of DD and increased PWV (Table 7-2), indexed LV mass, systolic and pulse pressure (all $p < 0.0001$), LV relative wall thickness ($p = 0.001$) and mean arterial pressure ($p = 0.02$).

Table 7-2 Median aortic PWV (interquartile range) according to age, gender and diastolic function grade

	Aortic PWV (m/s)			p-value
	Normal diastolic function	Grade I DD	Grade II-IV DD	
Women: 62-74 years	9.2 (8.2-10.1)	10.3 (8.9-12.1)	10.7 (8.4-13)	0.01
Women: 75+ years	9.6 (8.8-11.6)	10.7 (9.9-13.1)	12.6 (11.6-14.1)	0.002
Men: 62-74 years	9.6 (7.9-10.5)	10 (8.4-11.7)	12.3 (10.7-12.7)	0.005
Men: 75+ years	10.2 (9.3-10.9)	11.4 (10-13.7)	12.1 (9.7-12.9)	0.13

7.4.2 Association between age, gender and indices of arterial stiffness

The effects of age and sex on indices of aortic stiffness and selected parameters of LV structure and diastolic function are detailed in Table 7-3. There was a trend to suggest that age-associated differences in indices of arterial stiffness and LV remodelling and diastolic function were steeper in women than in men; PWV: $\beta = 0.19$ versus 0.11 m/s for each year, respectively; LV mass index: $\beta = 0.83$ versus 0.40 g/m² for each year, respectively; E/E_a: $\beta = 0.20$ versus 0.05 for each year, respectively; E_a: $\beta = -0.08$ versus -0.07 cm/s for each year, respectively.

Table 7-3 Association between of age, gender and indices of aortic stiffness, and selected parameters of LV structure and diastolic

	Association with age				Association with gender			Age-gender interaction
	Women		Men		Mean levels			
	rho	p-value	rho	p-value	Women	Men	p-value*	
PWV, m/s	0.41	<0.001	0.28	0.002	10.8	10.7	0.82	0.23
Brachial pulse pressure, mmHg	0.31	0.001	0.15	0.09	61	56	0.03	0.08
Central pulse pressure, mmHg	0.32	<0.001	0.19	0.04	53	46	0.001	0.31
Ea, cm/s	-0.23	0.02	-0.16	0.08	8.3	9.2	0.01	0.54
E/Ea	0.28	0.003	0.08	0.38	9.0	6.7	<0.001	0.09
Indexed LV mass, g/m ²	0.17	0.09	0.07	0.41	99	105	0.005	0.35
LV relative wall thickness	0.16	0.09	0.09	0.34	0.46	0.41	0.01	0.21

p-value for age-adjusted parameter differences(log-transformed when appropriate) between genders; Ea = lateral mitral annulus velocity; E/Ea = ratio of early mitral inflow velocity and lateral mitral annulus velocity

7.4.3 Association between arterial stiffness and diastolic function

Univariate associations between PWV and history of HT and diabetes mellitus, body mass index, LV mass index, E_a , E/E_a and diastolic function grade were stronger in women than in men (Table 7-4).

Table 7-4 Univariate associations between aortic PWV and clinical/echo parameters, stratified by gender

	Aortic PWV			
	Women		Men	
	rho	p-value	rho	p-value
Hypertension	0.33	<0.001	0.20	0.026
Diabetes	0.17	0.08	0.05	0.57
Coronary artery disease	0.12	0.23	0.13	0.13
Heart rate	0.14	0.16	0.07	0.41
Brachial systolic BP	0.47	<0.001	0.42	<0.001
Central systolic BP	0.46	<0.001	0.42	<0.001
Brachial diastolic BP	0.15	0.14	0.14	0.13
Central diastolic BP	0.16	0.10	0.16	0.08
Brachial pulse pressure	0.47	<0.001	0.40	<0.001
Central pulse pressure	0.48	<0.001	0.36	<0.001
Mean arterial pressure	0.38	<0.001	0.36	<0.001
Body mass index	0.31	0.001	0.03	0.77
E_a	-0.31	0.001	-0.16	0.07
E/E_a ratio	0.27	0.005	0.19	0.039
Indexed LV mass	0.25	0.009	0.07	0.46
LV ejection fraction	0.09	0.34	0.01	0.91
Diastolic function grade	0.44	<0.001	0.31	<0.001

The independent associations between PWV, diastolic function grade and significant covariates did not differ according to sex, and sex-pooled estimates are presented in (Table 7-5). After adjusting for age, sex, clinical risk factors, LV mass index and mean arterial pressure, the odds of DD were 22% higher with every 1 m/s increase in PWV. In contrast, neither brachial nor central pulse pressure was significantly associated with diastolic function grade in the multivariable models (Table 7-5).

Table 7-5 Association between indexed aortic PWV and diastolic dysfunction

	Odds Ratio	p-value
Aortic PWV (per 1 m/s)	1.22	0.001
Age (per 5 years)	1.39	0.005
Female gender	1.64	0.07
Hypertension	1.60	0.09
Diabetes	3.01	0.02
Indexed LV mass (per 5 g/m ²)	1.25	<0.0001

P>0.20: history of coronary artery disease, hyperlipidemia or smoking; body mass index; mean brachial artery pressure; brachial pulse pressure.

7.4.4 PWV and pulse pressure for the detection of diastolic dysfunction

PWV and pulse pressure performance did not vary according to sex for the detection of any DD (p = 0.38 and p = 0.06, respectively) or advanced DD (p = 0.44 and

$p = 0.33$, respectively). Sex-specific optimal discriminatory cut-offs were also similar for both sexes (Table 7-6). Accordingly, sex-pooled receiver-operator analyses were performed to compare the utility of PWV and pulse pressure for the detection of DD (Figure 7-1).

7.5 DISCUSSION

Our findings support the concept that increased aortic stiffness is associated with load-dependent alterations in diastolic function. Previously, most studies^{80, 85, 307} have investigated the relationship between arterial stiffness and diastolic function in clinic-based populations. More recently, Redfield et al.⁸⁶ demonstrated a positive association between advancing age, female sex and echocardiographic indices of vascular and ventricular stiffness in a community-based study. In this population-based study, a similar effect of female sex on the relationship between age, aortic stiffness and diastolic function was found. We have extended previous findings by confirming a direct association between PWV and diastolic function grade, which is independent of clinical-echocardiographic predictors of DD and distending arterial pressure. Additionally, we have shown that the overall performance of PWV to detect the presence of DD was superior to pulse pressure, a widely accepted surrogate measure of arterial stiffness.

7.5.1 Relationship between arterial stiffness and diastolic dysfunction

Since our data are cross-sectional, we are unable to determine the causal relationship between PWV and DD. Such a relationship, however, is biologically plausible and temporally feasible. Numerous potential pathways exist whereby increased aortic stiffness may result in DD. Stiffening of the aorta increases PWV,³¹⁰ resulting in the earlier return of wave reflection from the periphery to the proximal aorta, an augmentation of aortic systolic pressure and a decrease in aortic pressure during diastole.⁸¹ The resultant increase in afterload during LV systole and relative reduction in coronary perfusion during LV diastole may promote LV concentric

remodelling and hypertrophy^{311, 312} and retard LV relaxation²⁷⁵. In addition, development of subendocardial ischemia³¹³ may lead to further impairment of myocardial relaxation and promotion of interstitial fibrosis with a subsequent reduction in LV compliance³¹⁴ and global LV long axis systolic function⁸². Further, age-related increases in PWV appear to precede Doppler abnormalities in diastolic function. Numerous population-based studies in adults have shown that PWV rises at a constant rate up to the age of 40 years and then rises exponentially thereafter even in the absence of identifiable cardiovascular risk factors.^{180, 315} In contrast, the prevalence of any DD by echocardiography is rare prior to the age of 60 years in the absence of cardiovascular risk factors.^{20, 309} Longitudinal studies will be required to describe the natural history of diastolic function and determine whether individuals with increased PWV (or a greater rise in PWV over time) during middle age are more likely to develop DD and perhaps HF thereafter.

7.5.2 PWV versus pulse pressure as a marker of arterial stiffness

Although there is consensus that widened pulse pressure and increased PWV are both manifestations of aortic stiffness, the indices do not represent the same components of arterial function³¹⁰. Pulse pressure is dependent on the timing and amplitude of arterial wave reflection, and is therefore significantly influenced by characteristics such as heart rate and height as well as properties relating to arterial function. Furthermore, due to the phenomenon of pulse pressure amplification in peripheral arteries, brachial and aortic pressures may differ vastly, particularly in the younger adult, and the central BPs are proposed to be a more reliable measure of target organ load.³¹⁶ In contrast, PWV represents a measure of aortic stiffness that is

Table 7-6 Utility of aortic pulse wave velocity and brachial pulse pressure to detect diastolic dysfunction

	AUC (95%CI)	Optimal cut-off	Sens (%)	Spec (%)	LR+	LR-
Men: Any diastolic dysfunction (n=81)						
Aortic pulse wave velocity (m/s)	0.67 (0.58-0.77)	11.1	51	80	2.5	0.62
Brachial pulse pressure (mmHg)	0.52 (0.42-0.63)	64	31	78	1.4	0.89
Central pulse pressure (mmHg)	0.50 (0.41-0.59)					
Women: Any diastolic dysfunction (n=68)						
Aortic pulse wave velocity (m/s)	0.73 (0.64-0.83)	11.1	54	82	3.0	0.56
Brachial pulse pressure (mmHg)	0.67 (0.56-0.77)	65	51	79	2.5	0.61
Central pulse pressure (mmHg)	0.66 (0.56-0.74)	57	49	74	1.9	0.69
Men: Moderate or severe diastolic dysfunction (n=23)						
Aortic pulse wave velocity (m/s)	0.67 (0.54-0.80)	12.0	61	77	2.6	0.51
Brachial pulse pressure (mmHg)	0.64 (0.50-0.78)	66	48	82	2.6	0.64
Central pulse pressure (mmHg)						
Women: Moderate or severe diastolic dysfunction (n=27)						
Aortic pulse wave velocity (m/s)	0.74 (0.62-0.85)	11.9	67	78	3.0	0.43
Brachial pulse pressure (mmHg)	0.73 (0.62-0.84)	69	63	75	2.6	0.56
Central pulse pressure (mmHg)						

AUC = area under receiver operating characteristic curve; CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; Sens =sensitivity; Spec =specificity

The overall performance of PWV was superior to brachial pulse pressure (AUC: 0.70 versus 0.59, respectively; $p = 0.005$) and central pulse pressure (AUC: 0.70 versus 0.56, respectively; $p = 0.001$) for the detection of any DD. The poor performances of pulse pressures were due to the large overlap in subjects with normal diastolic function and those with mild diastolic function (Grade 1). No difference, however, existed in the utility of these indices of aortic stiffness for the detection of advanced DD ($p = 0.85$).

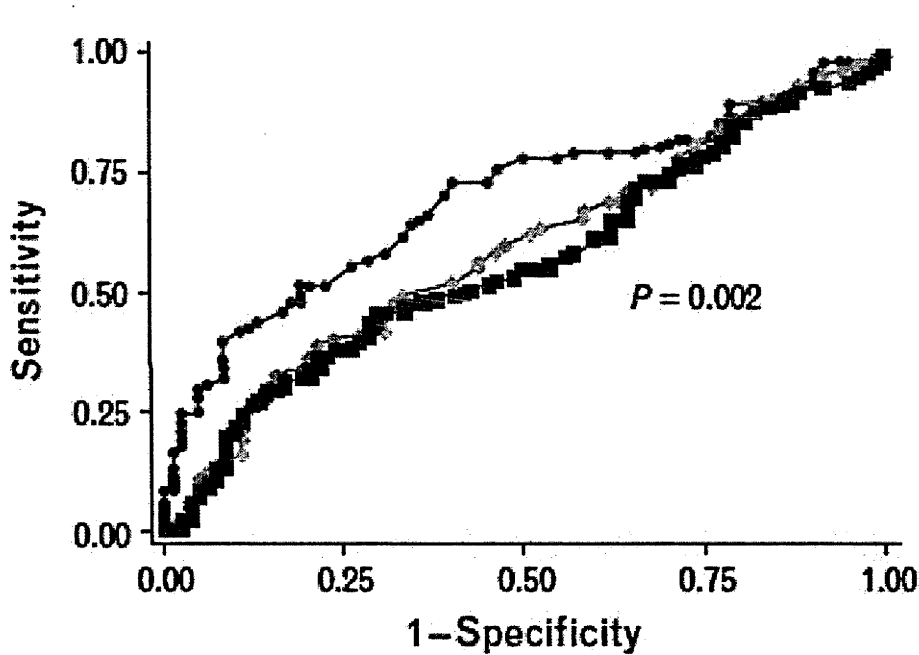


Figure 7-1 Comparison of overall performances of pulse wave velocity and pulse pressure for the detection of diastolic dysfunction.

Pulse wave velocity: area under receiver-operating characteristic curve (AUC) = 0.70. Brachial pulse pressure: AUC = 0.59. Central pulse pressure: AUC = 0.56.

independent of wave reflection.³¹⁰ To the best of our knowledge, this is the first study to compare the utility of pulse pressure and PWV for screening of LV dysfunction. We found that the value of PWV as a screening tool in this study was modest but superior to pulse pressure for the detection of preclinical DD, including 'mild' DD. Although early alterations in myocardial relaxation and LV filling have been clinically regarded as a part of the normal 'ageing' process, recent findings have highlighted the importance of LV diastolic function as a robust and independent marker of increased risk of death in community-based adults.²⁰ Consistent with previous studies¹⁸¹ showing an age-related loss of peripheral pressure amplification, we found that there was low pulse pressure amplification between central and brachial BPs in this sample of older adults. Accordingly, estimation of central pressures using applanation tonometry did not improve the performance of pulse pressure for the identification of subjects with DD.

7.5.3 Implications

Our results have important clinical and methodological implications. First, since PWV is modifiable with medical therapy,^{317, 318} its value as an intermediate outcome for future therapeutic studies on patients with DD or HF should be determined. Perhaps more importantly, strategies incorporating PWV as a tool for the identification of subjects with increased aortic stiffness should be considered in primary prevention studies of DD, a condition associated with adverse prognosis in the community.²⁰ Second, the association between female sex and age-associated increases in aortic stiffness, concentric LV remodelling and Doppler parameters of

LV relaxation and filling pressure may at least partly account for the consistent observation of preponderance of women in community-based studies^{54, 308} of HF with preserved EF. Finally, future studies assessing the incremental value of PWV as a risk marker for the development of adverse cardiovascular outcomes such as congestive HF, atrial fibrillation and cardiovascular death should adjust for the potential intermediary effects of DD.

7.5.4 Limitations

Several potential limitations should be considered when interpreting our results. The study population was not ethnically diverse (97% white) and the association between PWV and diastolic function was determined using cross-sectional data. Thus, further work is required to confirm our results in other population groups and to delineate the temporal relationship between PWV and diastolic function. The majority of our sample was treated chronically with antihypertensive medications that may differentially modify indices of aortic stiffness and DD and alter the true relationship between these physiological risk markers. Given that a decrease in PWV to BP reduction is, however, more likely to be related to change in distending pressure than to the effects on aortic stiffness, one could argue that the relationship between PWV and DD could be attenuated in patients on vasoactive medication. Further, with the widespread prescription of antihypertensive medications in older adults, such a limitation is unavoidable in population-based studies.

7.5.5 Conclusion

Our results suggest that age-related deterioration in DD is independently associated with increasing aortic stiffness and appears to be more prominent in women than in

men. PWV, but not pulse pressure, was related to diastolic function grade, independent of clinical-echocardiographic predictors of DD and distending arterial pressure. The overall utility of PWV to identify preclinical DD was superior to pulse pressure. Studies are required to evaluate whether modification of PWV with medical therapy is associated with attenuation of risk for the development of DD and adverse cardiovascular events such as congestive HF and atrial fibrillation.

Chapter 8: CONCLUSIONS AND FUTURE DIRECTIONS

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8.1 CONCLUSION

Results of this thesis have advanced the knowledge of cardiovascular epidemiology on a number of fronts, specifically in the fields of HF and left ventricular dysfunction.

On the national front, the Canberra Heart Study is the first Australian study to carefully evaluate the prevalence of HF and left ventricular systolic dysfunction in the community. Our results show that HF rates and the proportion of the population are similar to estimates in the United States and Western Europe. Personal communication with HF researchers and health policy advisors would indicate that this information is being used as it was anticipated; to guide health policy with regards to service delivery and illness care interventions at the individual level; and to plan illness care primary preventative interventions at the population level in order to reduce the burden of HF in our community.

On the international front, the Canberra Heart Study has provided important data on the epidemiology of DD in the community, and our results are being used to inform expert opinions³¹⁹ and taskforce guidelines.⁶⁴ In particular, our robust echocardiographic methods and high response rates are likely to increase internal validity of results when compared to previous international efforts that either had inadequate echocardiographic assessment for the assessment of diastolic function (with the increased potential for “non-systematic” misclassification) or suffered from poor response rates that increase the potential for selection bias. Our study shows that DD is common in the community and is frequently unaccompanied by overt symptoms and signs of HF. Despite the absence of symptoms, individuals with

advanced DD-NEF have accompanying structural abnormalities that reflect an increased risk for adverse cardiovascular outcomes and have a reduced quality of life.

We have used cross-sectional data to assess the clinical characteristics of subjects with left ventricular dysfunction. Obviously, these data will not be able to be used to establish causality, as the temporal relationship between “risk” exposure and left ventricular dysfunction cannot be evaluated in a “snap-shot” observation. Nonetheless, identification of the clinical characteristics of subjects with prevalent left ventricular dysfunction has provided an epidemiological insight into disease causality. This information will be used in future research efforts such as the assessment of a screening program. In general, the cost-effectiveness of screening is likely to be optimised when high-risk subgroups are targeted. Our results would indicate that members of the general population who are at higher risk of preclinical left-ventricular systolic dysfunction include older persons, men, patients with a history of myocardial infarction, and probably patients with diabetes mellitus. Clinical predictors of DD, which was mostly present without overt HF, include ischaemic heart disease and risk factors for cardiovascular disease such as older age; increased systemic BP and a history of HT; diabetes mellitus; and obesity. It is likely that the burden of DD-NEF in the community will increase with our ageing population and increasing rates of obesity and diabetes in the community. Whether this burden can be reduced by screening efforts remains to be determined. Our observations suggest that, since preclinical advanced DD-NEF is relatively common and associated with cardiac markers that portend a poor cardiovascular prognosis,

screening efforts may be warranted. Furthermore, since DD-NEF is rare in subjects without comorbid cardiovascular conditions, the efficiency of screening programs should be optimised by targeting high-risk groups, defined according to age (>70 years) and/or risk factor status (HT, ischaemic heart disease, diabetes or obesity).

At present, access to an assessment with transthoracic echocardiographic is very limited, largely due to workforce issues (undersupply of cardiac sonographers) and to a lesser extent related to supplier-related economic considerations (high recurrent costs relating to sonographer wages; considerable cost of echocardiography machines and reporting systems which need to be updated every 3-5 years) relative to income (largely predicated by the Medicare rebate for each study). Accordingly, the ability to provide an echocardiographic service for patients who have few, if any, symptoms or signs of overt cardiovascular disease would not be feasible even in a world that is not confronted with the realities of economic scarcity from the perspective of the government and taxpayer. The availability of a cheaper, more accessible, and well-tolerated non-invasive test that could serve as a filter prior to referral for echocardiography may be able to identify individuals with early myocardial dysfunction. We have assessed the diagnostic performances of 2 such investigations; the NT-pro-BNP levels, and pulse wave analysis.

NT-proBNP levels are clearly related to both systolic and diastolic LV function in the general community, but are also influenced by other important factors that are known risk markers of adverse cardiovascular outcomes, such as renal disease and left ventricular hypertrophy without measurable myocardial dysfunction. Indeed, NT-proBNP may be a good integrative marker of cardiac stressors rather than simply

a measure of left ventricular dysfunction, and therefore may provide incremental information beyond echocardiographic assessment. This needs to be assessed in future studies.

Our results suggest that age-related deterioration in DD is independently associated with increasing PWV, an index of aortic stiffness. However, the overall utility of PWV to identify preclinical DD was marginal. Because of the relatively low specificity of PWV to detect even advanced DD, one could not recommend this test as a filter prior to referral for echocardiography unless further studies show that such an approach could assist with the provision of “personalised medicine”, in which patient management is guided by their own physiological measures rather than generic recommendations based on secular trends. This topic needs to be addressed by future clinical studies.

8.2 FUTURE DIRECTIONS

To establish whether Stage B HF (preclinical left ventricular dysfunction) is a condition that would be suitable for screening:

- i. The disease represents a serious condition. Clearly HF is a serious condition that is worthy of screening (see review in Chapter 1);
- ii. The condition is detectable in the preclinical phase of the disease. We and others have now shown that LV diastolic and systolic dysfunction is detectable in persons who have no overt symptoms of HF;

- iii. There is a critical phase during the detectable preclinical stage during which treatment is beneficial; there is only very limited evidence, which is restricted to persons with reduced EF, to support this assertion (Chapter 1).

Several important questions have been raised by our results and need to be addressed by future studies in order to support a screening program for LV dysfunction. These include:

- i. What is the relationship between preclinical left ventricular dysfunction and the risk of death and incident cardiovascular events such as HF and atrial fibrillation? With the ability to detect preclinical left ventricular dysfunction with echocardiography, more work is required to establish the clinical risk associated with early myocardial dysfunction, and whether this risk can be ameliorated by early intervention strategies such as the lowering of BP.
- ii. What is the optimal method of screening for preclinical left ventricular dysfunction? We have avoided the obvious temptation to address this question using our cross-sectional study in which prevalent cases of preclinical left ventricular dysfunction have been identified using echocardiography. Rather, it would be preferable to assess a screening program that identifies incident disease in subsequent assessments of this cohort in order to avoid overestimation of the performance of the screening test.

Even if the pre-conditions for an efficacious screening program are established for left ventricular dysfunction, scarcity of resources will necessitate the need for a

formal economic evaluation of such a screening program prior to its widespread adoption in order to address the fundamental issue of “at what cost?”.³²⁰

We have received funding from the National Heart Foundation of Australia to continue the Canberra Heart Study as a prospective cohort study. Response rates are over 90%, and data collection will be completed by 2010. At present, we only have preliminary data to report. In 2008, we assessed mortality rates of subjects with DD without a history or clinical evidence of HF. During a mean follow-up of 4.8 years, there were 61 deaths in preclinical subjects with $EF \geq 50\%$. Death rates among individuals with normal LV diastolic function and mild DD were similar (0.8 v 1.1 per 100 person-yrs, respectively; $p=0.24$). However, the rate of death among those with advanced DD (3.0 per 100 person-yrs) was higher when compared to subjects with normal diastolic function and mild DD ($p<0.01$ for both) (Figure 8-1).

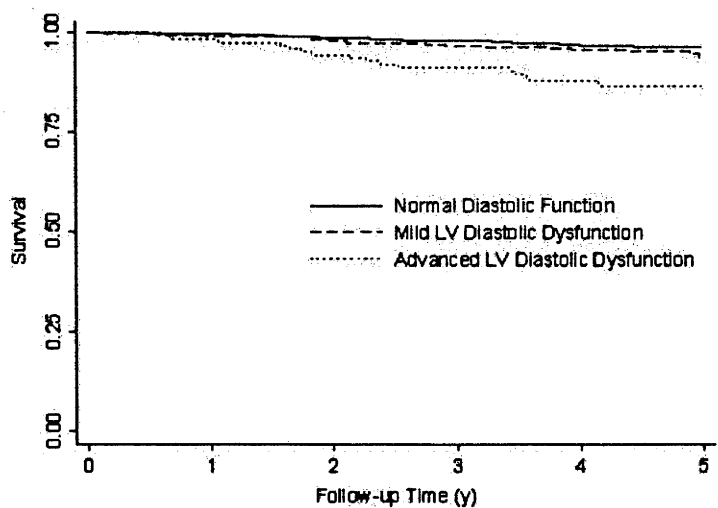


Figure 8-1 Survival in preclinical subjects with $EF \geq 50\%$, according to baseline diastolic function.

After adjustment for age, sex, EF and cardiovascular risk factors, preclinical advanced DD was associated with an increased mortality risk (adjusted Hazards Ratio 2.2, CI 1.1 to 4.2).

We anticipate that our ongoing Canberra Heart Study will continue to provide novel data to address the highlighted gaps in knowledge in this field of cardiovascular epidemiology. Such information is essential if we are to evolve from the current paradigm of healthcare that is focused on the treatment of individuals with disease to a paradigm directed at disease prevention at the population-level in order to maintain the health and well-being of individuals (Figure 8-2).

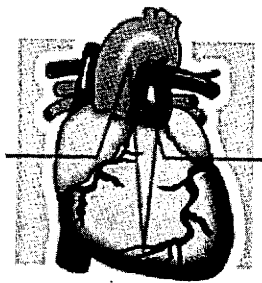
上医医未病之病
中医医将病之病
下医医已病之病
~ 黄帝内经 ~

Figure 8-2 The Superior Doctor: extract from 1st Chinese Medical Text.

“The superior doctor prevents sickness; the mediocre doctor attends to impending sickness; the inferior doctor treats actual sickness”: Attributed to Huang Dee Nai-Chan, circa 2600BC.

APPENDIX A: SELF ADMINISTERED QUESTIONNAIRE

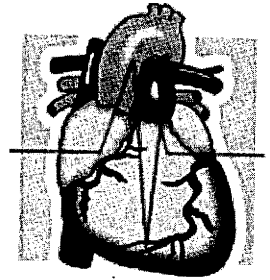
CANBERRA HEART STUDY



2002

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Questionnaire A

Dear Title Surname,

To help us understand more about the relationship between certain personal characteristics and heart failure, we would like to ask you some questions about your general health, past medical history, education and occupation history.

All questions should be answered unless indicated otherwise. Please return the questionnaire when you attend the 'assessment clinic' at the Canberra hospital.

You may be assured of complete confidentiality.

If you have any queries please do not hesitate to call one of our research nurses (phone: 62443762).

Thank you for your assistance,

Dr Walter Abhayaratna
Cardiology Fellow
Chief Investigator

Put a tick ☒ in the most appropriate box

1

Years

--	--

2

Aboriginal or
Torres Strait
Islander origin

Neither	
Aboriginal	
Torres Strait Islander	
Both	

3

Country of birth

Australia
UK and Ireland
Italy
Greece
Germany

→Go to Q5

Netherlands
New Zealand
Vietnam
Poland

--

4

Year of arrival in Australia

--	--	--	--

The following questions relate to your health.

5

In general,
would you say

Excellent	<input type="checkbox"/>
Very good	<input type="checkbox"/>
Good	<input type="checkbox"/>
Fair	<input type="checkbox"/>
Poor	<input type="checkbox"/>

6

Compared to one year ago, how would you rate your health
in general now?

Much better now than one year ago	<input type="checkbox"/>
Somewhat better now than one year ago	<input type="checkbox"/>
About the same as one year ago	<input type="checkbox"/>
Somewhat worse now than one year ago	<input type="checkbox"/>
Much worse now than one year ago	<input type="checkbox"/>

7

The following questions are about activities you might do during a
typical day. Does your health now limit you in these activities? If so,
how much?

(Circle one number on each

ACTIVITIES	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited At All
a. Vigorous activities , such as running, lifting objects, participating in strenuous sports	1	2	3
b. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than one kilometre	1	2	3
h. Walking half a kilometre	1	2	3
i. Walking 100 metres	1	2	3
j. Bathing or dressing yourself	1	2	3

8

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Circle one number on each line)

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

9

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle one number on each line)

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

10

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	<input type="checkbox"/>
Slightly	<input type="checkbox"/>
Moderately	<input type="checkbox"/>
Quite a bit	<input type="checkbox"/>
Extremely	<input type="checkbox"/>

11

How much bodily pain have you had in the past 4 weeks?

No bodily pain	
Very mild	
Mild	
Moderate	
Severe	
Very severe	

12

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	
A little bit	
Moderately	
Quite a bit	
Extremely	

13

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(Circle one number on each

	All of the time	Most of the time	A Good Bit of the Time	Some of the time	None of the time
a. Do you feel full of life?	1	2	3	4	5
b. Have you been a very nervous person?	1	2	3	4	5
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d. Have you felt calm and peaceful?	1	2	3	4	5
e. Did you have a lot of energy?	1	2	3	4	5
f. Have you felt down?	1	2	3	4	5
g. Did you feel worn out?	1	2	3	4	5
h. Have you been a happy person?	1	2	3	4	5
i. Did you feel tired?	1	2	3	4	5

14

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	<input type="text"/>
Most of the time	<input type="text"/>
Some of the time	<input type="text"/>
A little of the time	<input type="text"/>
None of the time	<input type="text"/>

15

How TRUE or FALSE is each of the following statements for you?

(Circle one number on each)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

16

Do you consider yourself to be-

Acceptable weight	<input type="text"/>
Underweight	<input type="text"/>
Overweight	<input type="text"/>
Don't know	<input type="text"/>

The following questions relate to the physical activity you did IN THE LAST WEEK.

17

IN THE LAST WEEK how many times have you walked continuously, for at least 10 minutes, for recreation, exercise or to get to or from places?

Number

(If 'none' go to Q19)

18

What do you estimate was the total time that you spent walking in this way IN THE LAST WEEK?

In Hours and / or minutes

Hours

Minutes

19

IN THE LAST WEEK how many times did you do any **vigorous** gardening or heavy work around the yard that made you breathe harder or puff or pant?

Number

(If 'none' go to Q21)

20

What do you estimate was the total time that you spent doing vigorous gardening or heavy work around the yard IN THE LAST WEEK?

Hours

Minutes

The following questions **EXCLUDE** household chores or gardening or yardwork.

21

IN THE LAST WEEK, how many times did you do any **vigorous** physical activity that made you breathe harder or puff and pant? (e.g. jogging, cycling, aerobics, competitive tennis, etc.)

Number

(If 'none' go to Q23)

22

What do you estimate was the total time that you spent doing this **vigorous** physical activity IN THE LAST WEEK?

Hours

Minutes

The following questions **EXCLUDE** household chores or gardening or yardwork.

23

IN THE LAST WEEK, how many times did you do any other more MODERATE physical activity that you haven't already mentioned? (e.g.

Number

(If 'none' go to Q25)

24

What do you estimate was the total time that you spent doing these activities IN THE LAST WEEK?

Hours

Minutes

The following questions are about your average **WEEKLY** level of activity **IN THE LAST SIX MONTHS.**

25

On average, IN THE LAST SIX MONTHS how much time did you spend each week walking for recreation/exercise or to get to or from places? (THIS IS WALKING CONTINUOUSLY FOR AT LEAST 10 MINUTES)

Hours

Minutes

The following questions **EXCLUDE** household chores or gardening or yardwork.

26

On average, IN THE LAST SIX MONTHS how much time did you spend each week doing **vigorous** physical activity which made you breathe harder or puff and pant? (e.g. jogging, cycling, aerobics, competitive tennis, etc.)

Hours

Minutes

27

On average, IN THE LAST SIX MONTHS how much time did you spend each week doing any other more moderate physical activity that you haven't already mentioned (e.g. gentle swimming, social tennis, golf, etc)

Hours

Minutes

The next few questions relate to smoking and alcohol habits.

28

Have you ever smoked cigarettes, cigars or a pipe regularly, that is, every day?

Yes	<input type="checkbox"/>	→At what age did you start smoking regularly?	<input type="text"/>	<input type="text"/>	years
No	<input type="checkbox"/>	→Go to Question 32			

29

Have you given up smoking?

Yes	<input type="checkbox"/>	→When did you last give up smoking?	<input type="text"/>	<input type="text"/>	years ago
No	<input type="checkbox"/>	→Go to Question 31			

30

Prior to giving up smoking, how much did you smoke?

Manufactured cigarettes per day	<input type="text"/>	<input type="text"/>	<input type="text"/>
Grams "hand-rolled" per week	<input type="text"/>	<input type="text"/>	<input type="text"/>
Cigars per week	<input type="text"/>	<input type="text"/>	<input type="text"/>
Grams pipe tobacco per week	<input type="text"/>	<input type="text"/>	<input type="text"/>

→Go to Question 32

31

If currently smoking: How much do you usually smoke?

Manufactured cigarettes per day	<input type="text"/>	<input type="text"/>	<input type="text"/>
Grams "hand-rolled" per week	<input type="text"/>	<input type="text"/>	<input type="text"/>
Cigars per week	<input type="text"/>	<input type="text"/>	<input type="text"/>
Grams pipe tobacco per week	<input type="text"/>	<input type="text"/>	<input type="text"/>

32

How many days a week would you usually have an alcoholic drink NOW?

Never	<div></div>	→Go to Question 35
Less than once a week	<div></div>	
1-2 days a week	<div></div>	
3-4 days a week	<div></div>	
5-6 days a week	<div></div>	
Every day	<div></div>	

33

What do you mostly drink?

Light beer	<div></div>
Beer	<div></div>
Wine	<div></div>
Spirit	<div></div>
Other	<div></div>

34

On the days when you have a drink, how many drinks do you usually have?

13 or more drinks	<div></div>
9-12 drinks	<div></div>
5-8 drinks	<div></div>
3-4 drinks	<div></div>
1-2 drinks	<div></div>

35

Has there been a period in your life when you drank quite a bit more than you do now?

Yes	<div></div>	→How many years ago?	<div></div> <div></div> years
No	<div></div>		
Don't know	<div></div>		

The next few questions relate to your caffeine intake.

36

Do you drink tea?

Yes	<input type="text"/>	→How many cups per day?	<input type="text"/> <input type="text"/>	cups
No	<input type="text"/>	→Go to Question 39		

37

How do you usually make your tea?

Teabags	<input type="text"/>
Tealeaves	<input type="text"/>
Both	<input type="text"/>

38

Do you drink coffee?

Yes	<input type="text"/>	→How many cups per day?	<input type="text"/> <input type="text"/>	cups
No	<input type="text"/>	(excluding DECAFFEINATED)		
		→Go to Question 40		

39

How do you usually make your coffee?

Instant	<input type="text"/>
Percolated	<input type="text"/>
Both	<input type="text"/>

The following questions are about specific health conditions.

40 Has a doctor ever told you that you have heart failure (a weak heart)?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

→ Go to Question 45

41 How old were you when you were first diagnosed with heart failure?

Years	<input type="text"/>	<input type="text"/>
-------	----------------------	----------------------

42 Do you currently have heart failure?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

43 Are you currently on any treatment for heart failure?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

44 Have you ever been **admitted** to a hospital for treatment of heart failure?

Yes	<input type="checkbox"/>	→How many times?	<input type="text"/>	<input type="text"/>
No	<input type="checkbox"/>			
Don't know	<input type="checkbox"/>			

Has a doctor ever said that you have any of the following conditions?

CONDITION	No	Don't know	Yes→	Age when first told	Years of treatment
Anaemia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Angina	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Osteoarthritis / Rheumatoid arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Coronary artery disease (narrowing in the heart artery / arteries)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Asthma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Chronic bronchitis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Cancer: which type(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Emphysema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Heart attack(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
High blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
High Cholesterol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Gout	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Rheumatic fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Peripheral vascular disease (narrowings in the leg or arm artery / arteries)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Sleep apnoea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
'Mini-stroke'	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Stroke	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Thyroid condition	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

The following section asks about your education and employment status.

46

What is the highest level you reached at school? If educated overseas record equivalent.

No schooling	<input type="checkbox"/>
Some primary	<input type="checkbox"/>
Completed primary	<input type="checkbox"/>
Some secondary	<input type="checkbox"/>
Completed intermediate/school certificate (Year 10)	<input type="checkbox"/>
Completed leaving / higher school certificate (Year 12)	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

47

Have you completed a trade certificate or any other educational qualification since leaving school?

No	<input type="checkbox"/>	→ Go to Q 49
Still studying for first qualification	<input type="checkbox"/>	→ Go to Q 49
Yes	<input type="checkbox"/>	→ Go to Q 48

48

Which of these categories best describes the highest qualification you have completed since leaving school?

Trade Certificate/Apprenticeship	<input type="checkbox"/>	Associate Diploma	<input type="checkbox"/>
Technician's Certificate/ Advanced	<input type="checkbox"/>	Undergraduate Diploma	<input type="checkbox"/>
Nursing Certificate (Enrolled Nurse)	<input type="checkbox"/>	Bachelor Degree	<input type="checkbox"/>
Nursing Certificate (Registered Nurse)	<input type="checkbox"/>	Postgraduate Diploma	<input type="checkbox"/>
Teaching Certificate	<input type="checkbox"/>	Masters Degree/ Doctorate	<input type="checkbox"/>
Other Certificate	<input type="checkbox"/>	Other (specify)	<input type="checkbox"/>

49

What is your employment status?

Employed
Unpaid work for family business
Home-maker/housewife
Never worked
Retired
Social security/disability pension

	→Go to Q 50
	→Go to Q 50
	→Go to Q 53
	→Go to Q 54
	→Go to Q 52
	→Go to Q 52

50

How many hours a week do you usually work in (all) your job(s)?

Hours		
Don't know		

51

Main
occupation?

--

→Go to Q 53

52

Prior to retirement, what was your main occupation?

Occupation (specify)

--

53

Could you list other jobs that you have held for a period of over 5 years, and state the **approximate** age at which you commenced each job.

Position	Age at commencement

The next section asks about members of your household.

54 What is your marital status

Married	<input type="checkbox"/>	→ Go to Q 55
De facto	<input type="checkbox"/>	→ Go to Q 55
Separated	<input type="checkbox"/>	→ Go to Q 55
Divorced	<input type="checkbox"/>	→ Go to 'Q 63'
Widowed	<input type="checkbox"/>	→ Go to Q 55
Never married	<input type="checkbox"/>	→ Go to 'Q 63'

55 What is the highest level that your spouse/partner reached at school?

No schooling	<input type="checkbox"/>
Some primary	<input type="checkbox"/>
Completed primary	<input type="checkbox"/>
Some secondary	<input type="checkbox"/>
Completed intermediate/school certificate (Year 10)	<input type="checkbox"/>
Completed leaving / higher school certificate (Year 12)	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

56 Has your spouse/partner completed a trade certificate or any other educational qualification since leaving school?

No	<input type="checkbox"/>	→ Go to Q 58
Still studying for first qualification	<input type="checkbox"/>	→ Go to Q 58
Yes	<input type="checkbox"/>	→ Go to Q 57

57

Which of these categories best describes the highest qualification that your spouse/partner has completed since leaving school?

Trade Certificate/Apprenticeship	<input type="checkbox"/>	Associate Diploma	<input type="checkbox"/>
Technician's Certificate/ Advanced	<input type="checkbox"/>	Undergraduate Diploma	<input type="checkbox"/>
Nursing Certificate (Enrolled Nurse)	<input type="checkbox"/>	Bachelor Degree	<input type="checkbox"/>
Nursing Certificate (Registered Nurse)	<input type="checkbox"/>	Postgraduate Diploma	<input type="checkbox"/>
Teaching Certificate	<input type="checkbox"/>	Masters Degree/	<input type="checkbox"/>
Other Certificate	<input type="checkbox"/>	Other (specify)	<input type="checkbox"/>

58

What is your spouse's/partner's employment status?

Employed	<input type="checkbox"/>	→Go to Q 59
Unpaid work for family business	<input type="checkbox"/>	→Go to Q 59
Home-maker/housewife	<input type="checkbox"/>	→Go to Q 62
Never worked	<input type="checkbox"/>	→Go to Q '63'
Retired	<input type="checkbox"/>	→Go to Q 61
Social security/disability pension	<input type="checkbox"/>	→Go to Q 61

59

How many hours a week does your spouse/partner usually work in (all) his/her job(s)?

Hours	<input type="checkbox"/>	<input type="checkbox"/>
Don't know	<input type="checkbox"/>	<input type="checkbox"/>

60

What is your partner's main occupation?

Occupation (specify) →Go to Q 62

61

Prior to retirement, what was your partner's main occupation?

Occupation (specify)

62

Could you list other jobs that your spouse/partner has held for a period of over 5 years, and state the **approximate** age at which he/she commenced each job.

Position	Age at commencement

Would you like to make any comments?

63

Thank you for your participation.

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